# Central Nervous System (CNS)

## (PSYCHIATRY & NEUROLOGY)

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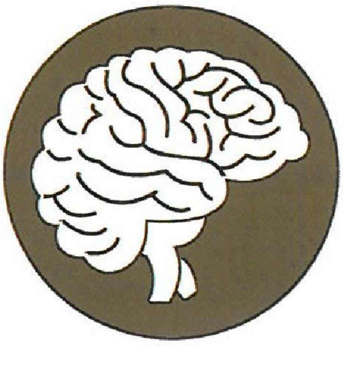
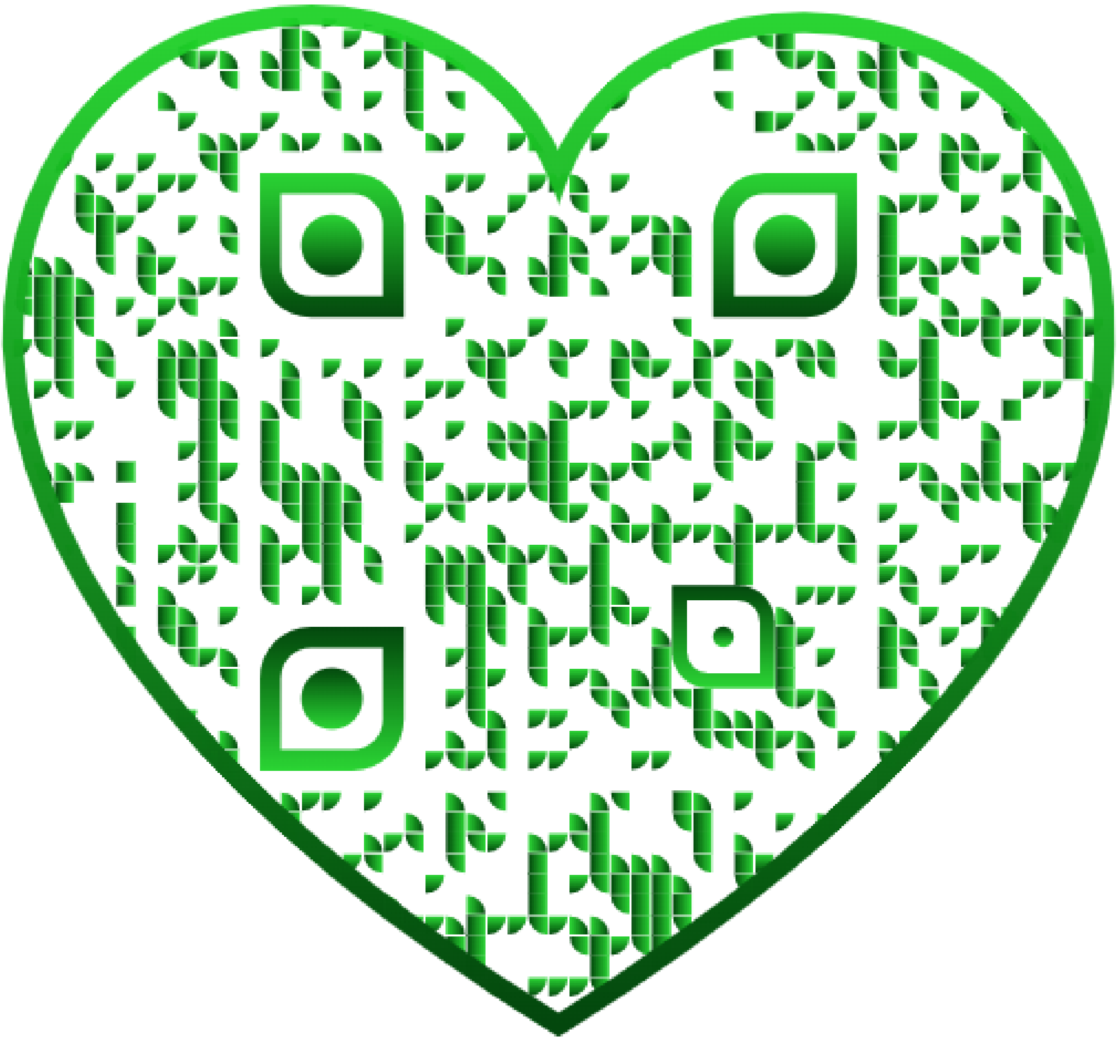
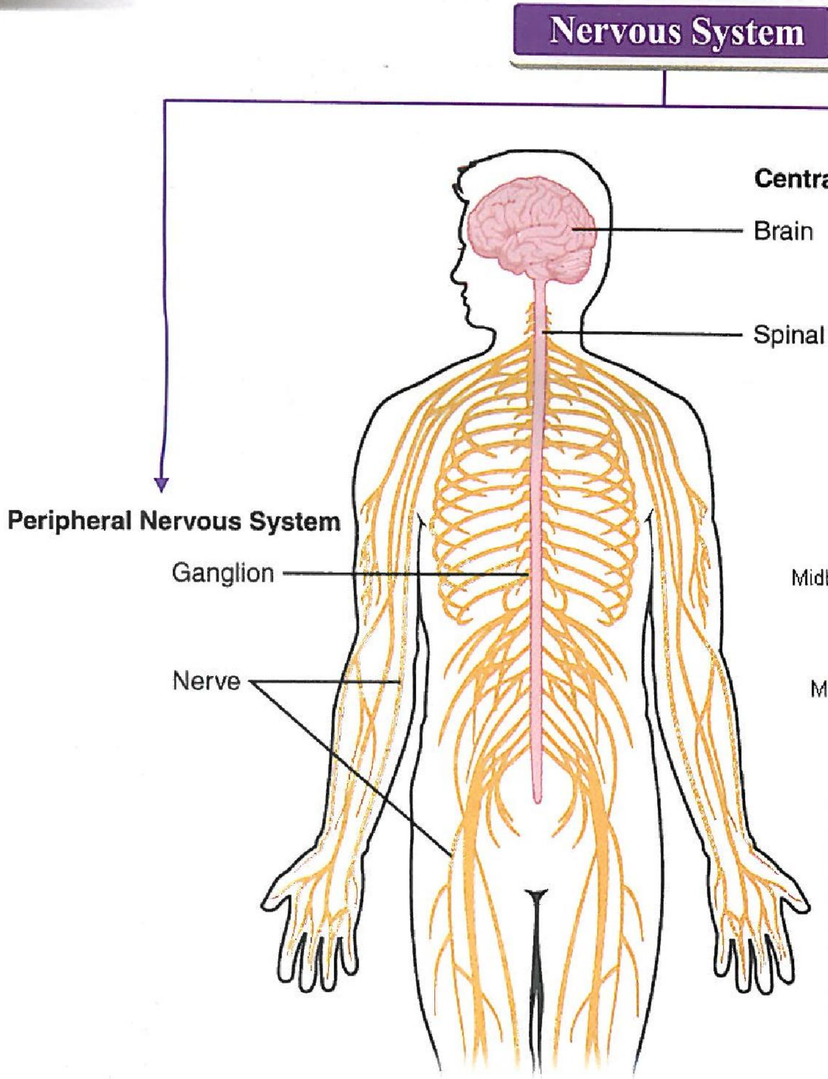
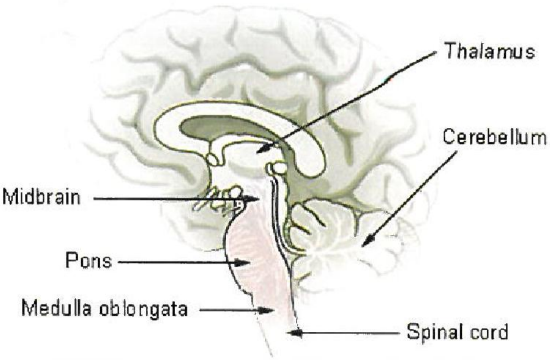


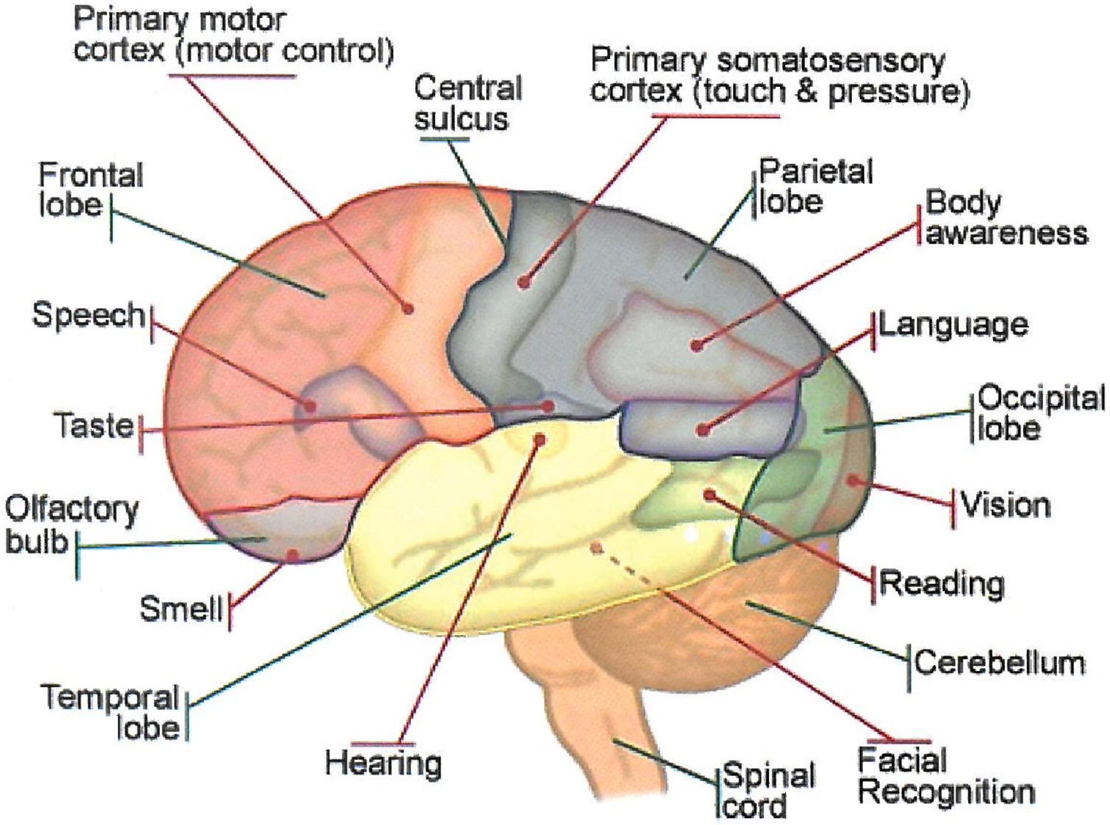


# Nervous System

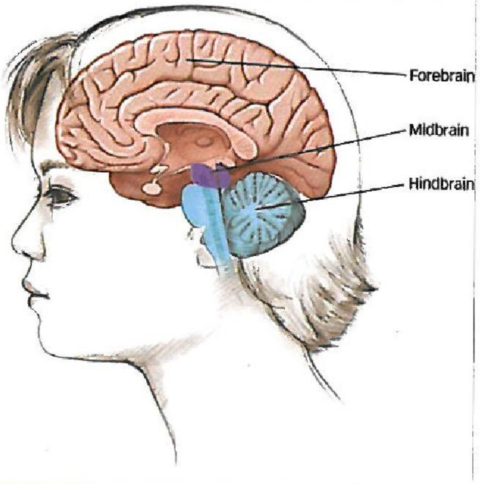

Central Nervous System
Brain
Spinal cord
Peripheral Nervous System
Ganglion
Nerve

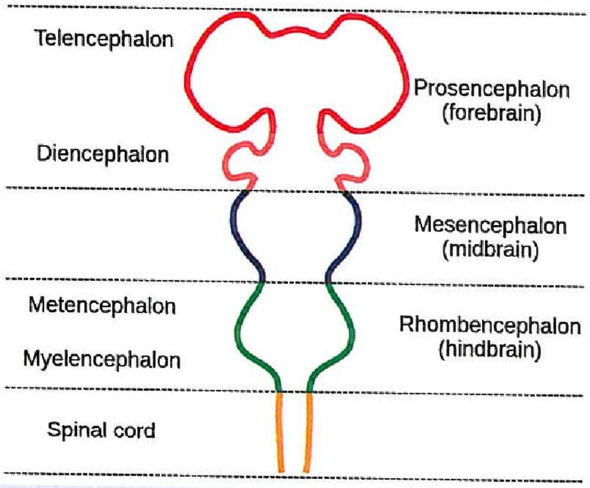

Thalamus
Cerebellum
Midbrain
Pons
Medulla oblongata
Spinal cord

- The central nervous system (CNS) is the part of the nervous system consisting of the brain and spinal cord.
- The central nervous system is so named because it integrates information it receives from, and coordinates and influences the activity of, all parts of the bodies.


Primary motor cortex (motor control)
Central sulcus
Primary somatosensory cortex (touch & pressure)
Frontal lobe
Parietal lobe
Body awareness
Speech
Language
Taste
Occipital lobe
Olfactory bulb
Vision
Smell
Reading
Cerebellum
Temporal lobe
Hearing
Spinal cord
Facial Recognition

# Brain Subdivision and Functions


Forebrain
Midbrain
Hindbrain


Telencephalon
Diencephalon
Prosencephalon (forebrain)
Mesencephalon (midbrain)
Metencephalon
Myelencephalon
Rhombencephalon (hindbrain)
Spinal cord

| | | | | | |
|---|---|---|---|---|---|
| **Central nervous system** | **Brain** | Prosencephalon | Telencephalon | Rhinencephalon, Amygdala, Hippocampus, Neocortex, Basal ganglia, Lateral ventricles | |
| | | | Diencephalon | Epithalamus, Thalamus, Hypothalamus, Subthalamus, Pituitary gland, Pineal gland, Third ventricle | |
| | | Brain stem | Mesencephalon | Tectum, Cerebral peduncle, Pretectum, Mesencephalic duct. | |
| | | | Rhombencephalon | Metencephalon | Pons, Cerebellum |
| | | | | Myelencephalon | Medulla oblongata |
| | Spinal cord | | | | |

**TELENCEPHALON (CEREBRUM)**

- Conscious thought processes, intellectual functions
- Memory storage and processing
- Conscious and subconscious regulation of skeletal muscle contractions

**DIENCEPHALON**

**THALAMUS**

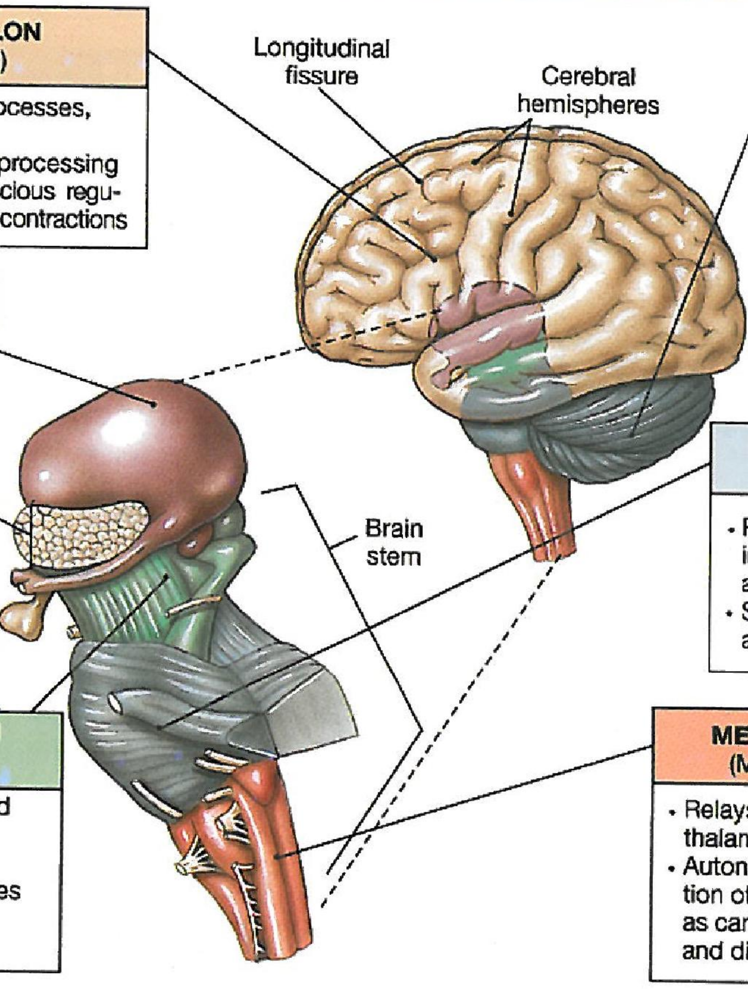
Relay and processing centers for sensory information

**HYPOTHALAMUS**

Centers controlling emotions, autonomic functions, and hormone production

**MESENCEPHALON (MIDBRAIN)**

- Processing of visual and auditory data
- Generation of reflexive somatic motor responses
- Maintenance of consciousness


Longitudinal fissure
Cerebral hemispheres
Brain stem

**METENCEPHALON (CEREBELLUM)**

- Coordinates complex somatic motor patterns
- Adjusts output of other somatic motor centers in brain and spinal cord

**METENCEPHALON (PONS)**

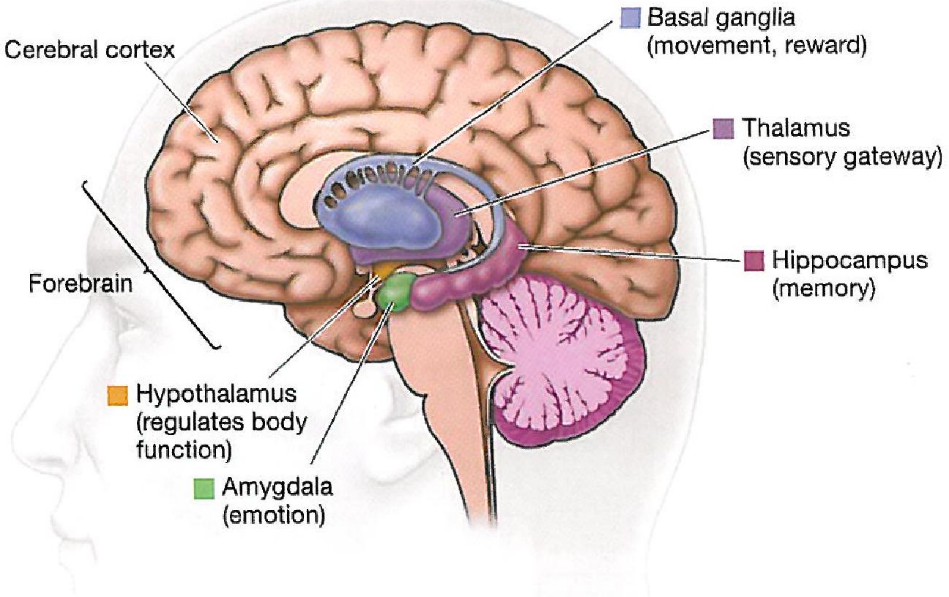
- Relays sensory information to cerebellum and thalamus
- Subconscious somatic and visceral motor centers

**MEDULLA OBLONGATA (MYELENCEPHALON)**

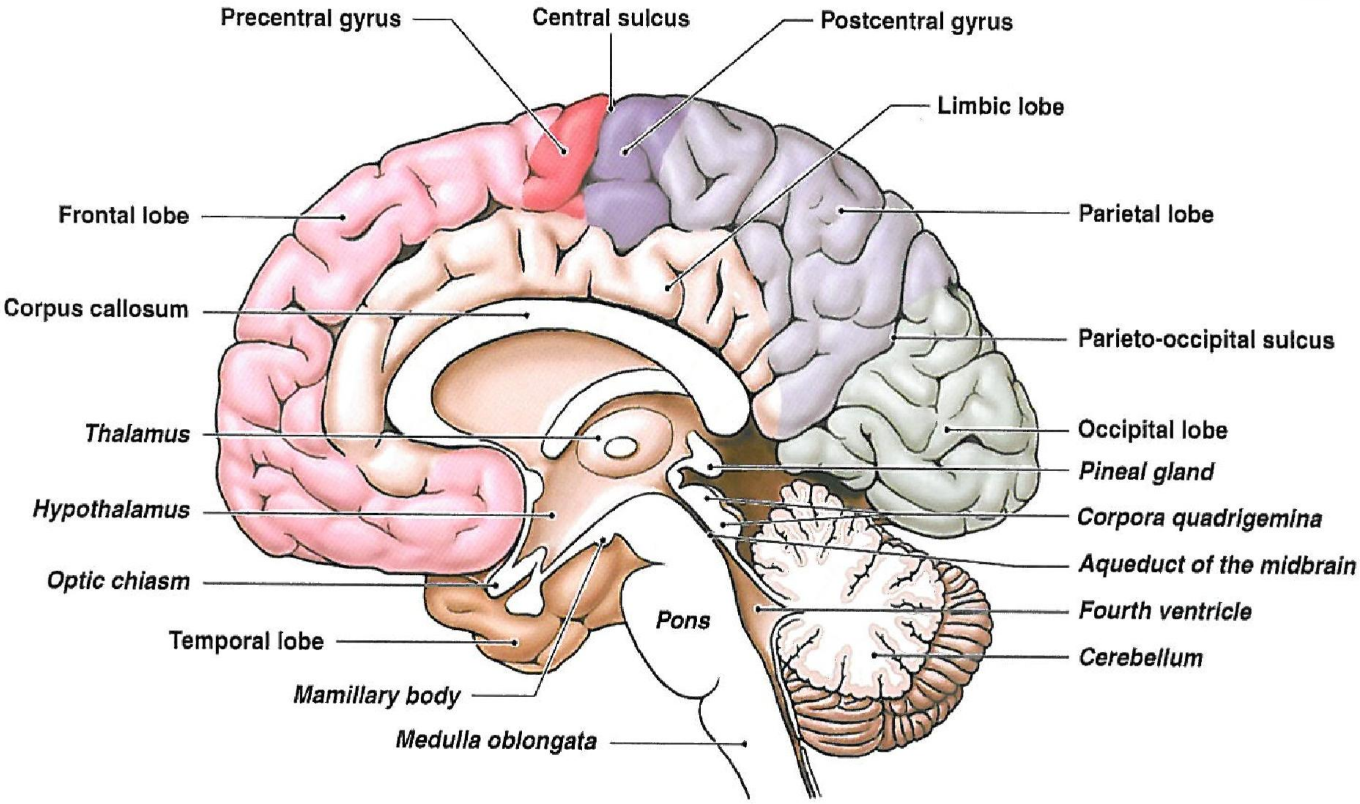
- Relays sensory information to thalamus
- Autonomic centers for regulation of visceral functions such as cardiovascular, respiratory, and digestive activities

## ➢ Forebrain (Prosencephalon):-

- The fore (front)-brain is the largest part of the brain.
- The most obvious structure of the forebrain is the **cerebrum**.
- The forebrain plays a central role in the processing of information related to complex cognitive activities, sensory and associative functions and voluntary motor activities.
- ***The forebrain separates into the***;
  - **Diencephalon**; thalamus, hypothalamus, epithalamus, and subthalamus.
  - **Telencephalon** which develops into the cerebrum. The cerebrum consists of the cerebral cortex, limbic system and the basal ganglia.


Cerebral cortex
Basal ganglia (movement, reward)
Thalamus (sensory gateway)
Forebrain
Hippocampus (memory)
Hypothalamus (regulates body function)
Amygdala (emotion)

| Subdivision | Functions |
|---|---|
| **Cerebral Cortex** | - The cerebral cortex is ***essential for*** **memory**, **attention**, **awareness**, **thought**, **language** and **consciousness**.<br>- It is commonly described as comprising three parts; **sensory**, **motor** and **association areas**, the cortex is ***connected to*** **thalamus** & **basal ganglia**. |
| **Basal Ganglia** | - The basal ganglia are associated with a variety of functions including: ***control of*** **voluntary motor movements**, **procedural learning**, **routine behaviours** or "habits" as bruxism, **eye movements**, **cognition** & **emotion**. |
| **Limbic System** | - It is ***not*** a **separate system** ***but*** a **collection of structures**.<br>- There are several important structures within the limbic system: amygdala, hippocampus, thalamus, hypothalamus, basal ganglia and cingulate gyrus and olfactory bulbs.<br>- The limbic system ***supports*** a variety of **functions** including; **epinephrine flow**, **emotion**, **behavior**, **motivation**, **long-term memory** and **olfaction**. |
| **Thalamus** | - The thalamus has multiple functions, some of its functions are **sensory processing** and regulation of consciousness, sleep and alertness. |
| **Hypothalamus** | - The hypothalamus is located below the thalamus, just above the brainstem and is part of the limbic system.<br>- It synthesizes and secretes certain neurohormones, often called ***releasing hormones*** or ***hypothalamic hormones***<br>- The hypothalamus ***controls*** **body temperature**, hunger, important aspects of parenting and attachment behaviours, thirst, fatigue, sleep and circadian rhythms. |


Precentral gyrus
Central sulcus
Postcentral gyrus
Limbic lobe
Frontal lobe
Parietal lobe
Corpus callosum
Parieto-occipital sulcus
Thalamus
Occipital lobe
Pineal gland
Hypothalamus
Corpora quadrigemina
Aqueduct of the midbrain
Optic chiasm
Fourth ventricle
Pons
Temporal lobe
Cerebellum
Mamillary body
Medulla oblongata

## ➢ Midbrain (Mesencephalon):-

- The midbrain is an area of the brain that is in the middle of two other regions: the forebrain and the hindbrain.
- It is located within the brainstem and between the two other developmental regions of the brain, the forebrain and the hindbrain.
- ***Function***; the midbrain serves important functions in **motor movement** and in **auditory** and **visual processing**.

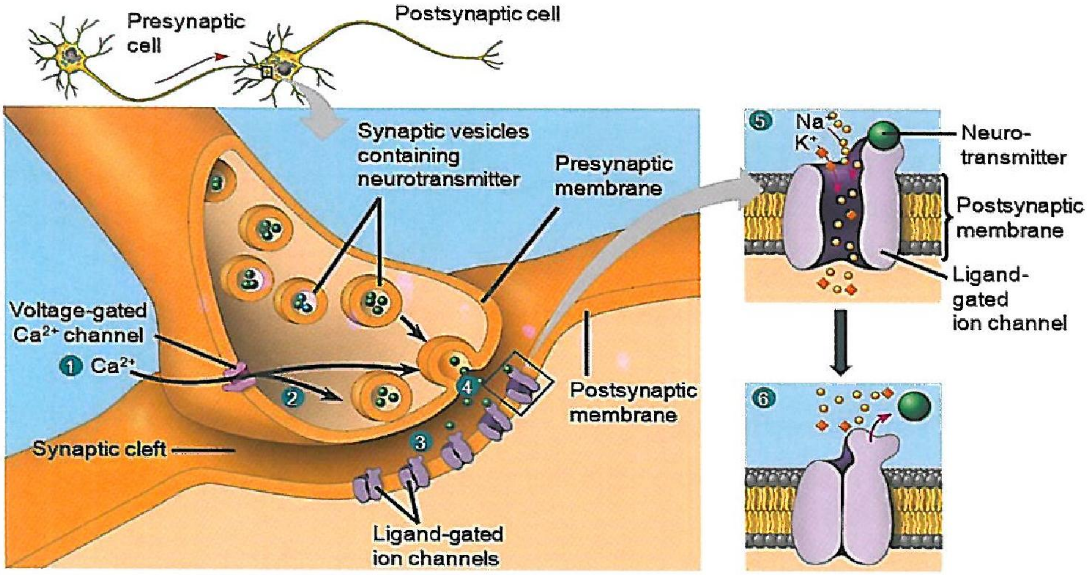
## ➢ Hindbrain (Rhombencephalon):-

- It includes the **medulla**, **pons** and **cerebellum**.

- **Cerebellum**;
  - The cerebellum (Latin for "***little brain***") is a region of the brain that plays an important role in ***motor control***.
  - The cerebellum coordinates **voluntary movements *such as* posture**, **balance**, **coordination** and **speech**, resulting in smooth and balanced muscular activity.
  - It is also important for learning motor behaviours.
- **Pons**;
  - In Latin, the word pons literally means ***bridge***.
  - It helps ***relay* messages** from the forebrain to the cerebellum.
  - ***Regulation* of respiration** (there are two centers in the pons that affect respiration).
  - ***Regulation* of sleep** and it has a role in **dreaming**.
- **Medulla Oblongata**;
  - It is located in the lower portion of the brainstem.
  - It is very important in **heart rate** and **blood pressure *control***.
  - It's responsible for multiple **autonomic** (involuntary) in the body such as **vomiting**, **sneezing** and **coughing**.

# Central Neurotransmitters

- The basic functioning of neurons in the CNS is similar to that of the autonomic nervous system (ANS). *For example*, transmission of information involves the release of neurotransmitters that diffuse across the synaptic space to bind to specific receptors on the postsynaptic neuron.
- The circuitry of the CNS is much more complex than that of the ANS, and the number of synapses in the CNS is far greater.
- The CNS, unlike the peripheral ANS, contains powerful networks of inhibitory neurons that are constantly active in modulating the rate of neuronal transmission. In addition, the CNS communicates through the use of multiple neurotransmitters, whereas the ANS uses only two primary neurotransmitters, acetylcholine and norepinephrine.


Presynaptic cell
Postsynaptic cell
Synaptic vesicles containing neurotransmitter
Presynaptic membrane
Voltage-gated Ca²⁺ channel
1 Ca²⁺
2
3
4
Synaptic cleft
Postsynaptic membrane
Ligand-gated ion channels
5
Na⁺
K⁺
Neuro-transmitter
Postsynaptic membrane
Ligand-gated ion channel
6

## ➢ Synaptic Potentials:-

- Synaptic potential refers to the ***difference*** in **voltage *between*** the **inside** and **outside** of a postsynaptic neuron. It is comes in ***three forms***;

**A) Excitatory Post-Synaptic Potentials (EPSPs)**;

- The EPSPs (***depolarize***) are generated by the following:
  1) Stimulation of an excitatory neuron causes the release of excitatory neurotransmitter molecules, such as glutamate or acetylcholine, which bind to receptors on the postsynaptic cell membrane. This causes a transient increase in the permeability of sodium ($Na^+$) ions.
  2) The influx of $Na^+$ causes a weak depolarization, or EPSP, that moves the postsynaptic potential toward its firing threshold.
  3) Stimulation of excitatory neurons increases, more excitatory neurotransmitter is released.

**B) Inhibitory Postsynaptic Potentials (IPSPs)**;

- The IPSPs (***hyperpolarize***) are generated by the following:
  1) Stimulation of inhibitory neurons releases inhibitory neurotransmitter molecules, such as γ-aminobutyric acid (GABA) or glycine, which bind to receptors on the postsynaptic cell membrane. This causes a transient increase in the permeability of specific ions, such as potassium ($K^+$) and chloride ($Cl^-$).
  2) The influx of $Cl^-$ and efflux of $K^+$ cause a weak hyperpolarization, or IPSP, that moves the postsynaptic potential away from its firing threshold.

**C) Combined effects of the EPSP and IPSP**;

- Most neurons in the CNS receive both EPSP and IPSP input.
- Several different types of neurotransmitters may act on the same neuron, but each binds to its own specific receptor. The overall action is the summation of the individual actions of the various neurotransmitters on the neuron.

- **Central Neurotransmitters:-**

# A) Amino Acids

## 1) Gamma (γ)-Aminobutyric Acid (GABA)

- **GABA** is the ***major*** **inhibitory neurotransmitters** (**NTs**) *in the* **CNS**, *including the* spinal cord.
- **GABA** ***receptors*** are divided into ***two main types***: **$GABA_A$** and **$GABA_B$**.
- Inhibitory postsynaptic potentials in many areas of the brain have a ***fast*** and ***slow*** **component**. The ***fast*** **component** is mediated by **$GABA_A$** ***receptors*** and the ***slow*** **component** by **$GABA_B$** ***receptors***.
- **$GABA_A$ receptors** are ***ionotropic receptors*** (***ligand gated ion channel***) that are ***selectively*** permeable to **$Cl^-$**. These receptors are ***selectively inhibited*** by **Picrotoxin** which cause generalized convulsions.
- **$GABA_B$ receptors** are ***metabotropic receptors*** (***G protein coupled receptors***), depending on their cellular location, either ***inhibit*** **$Ca^{2+}$ channels** or ***activate*** **$K^+$ channels**. These receptors are ***selectively activated*** by **Baclofen** (antispastic drug). Inhibitory postsynaptic potential is due to a selective increase in $K^+$ conductance.

## 2) Glycine

- ***Both*** **GABA** and **Glycine** are ***inhibitory*** **neurotransmitters**, which are typically released from local interneurons. Interneurons that release **glycine** are restricted to the **spinal cord** and **brainstem**.
- **Glycine receptors** (GlyR) that are ***selectively permeable*** to $Cl^-$. These receptors are ***selectively blocked*** by **Strychnine**, which is a potent spinal cord convulsant and has been used in some rat poisons.

## 3) Glutamate and Aspartate

- **Glutamate** and **Aspartate** are the ***major excitatory*** **neurotransmitter** in the brain.
- This excitation is caused by the ***activation*** of both **ionotropic** and **metabotropic receptors**.
- The **ionotropic receptors** can be further divided into ***three subtypes*** based on the action of selective agonists: α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA), kainic acid (KA) and **N-methyl-D-aspartate** (**NMDA**).
- The **metabotropic glutamate receptors** are **G protein-coupled receptors**.

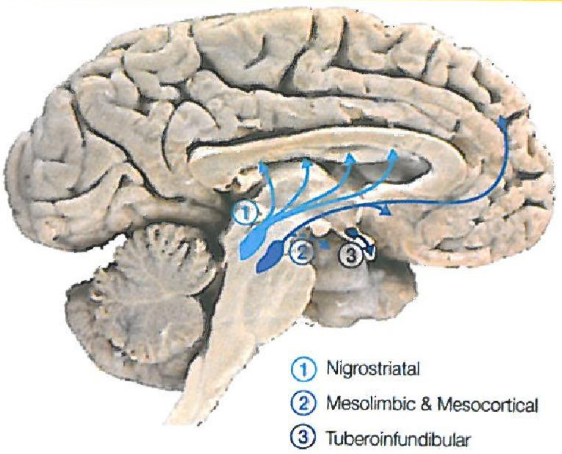
# B) Acetylcholine

- **Acetylcholine** was the ***first*** compound to be identified pharmacologically as a transmitter in the CNS.
- Most CNS responses to acetylcholine are mediated by a large family of G protein-coupled receptors.
- At a ***few sites***, acetylcholine causes slow ***inhibition*** of the neuron by activating the **$M_2$ receptor**.
- A ***far more widespread*** muscarinic action in response to acetylcholine is a slow ***excitation*** that in is mediated by **$M_1$ receptors**.
- Cholinergic pathways appear to ***play an important role*** in **cognitive functions**, ***especially*** **memory**.

# C) Monoamines

- **Monoamines** include the **catecholamines** (**Dopamine** and **Norepinephrine**) and **Serotonin**.
- Although these compounds are present in ***very small*** **amounts** in the CNS.

## 1) Dopamine



- The major pathways containing dopamine are 1) **substantia nigra** ***to the*** **neostriatum**, 2) **ventral tegmental** ***to limbic structures***, particularly the ***limbic cortex***, 3) **hypothalamus** ***to*** **pituitary gland**.
- **Dopamine** ***generally*** exerts a ***slow*** **inhibitory action** on CNS neurons ($D_2$).
- ***Five*** **dopamine receptors** have been identified, and they fall into two categories: $D_1$-like; $D_1$ & $D_5$ ($G_s$) and $D_2$-like; $D_2$, $D_3$ & $D_4$ ($G_i$). All dopamine receptors are **metabotropic**.
- **Parkinson's disease**; caused by a ***loss*** of dopamine-secreting neurons in an area of the **substantia nigra**.
- **Schizophrenia** involves ***altered*** **levels** of **dopamine activity**.

- ***SRT Steps***;
    1) **Find Sleep Threshold**; by determined the average minimum amount of time to able to sleep (*for example*; 3 hours).
    2) **Sleep Restriction**; by stay awake for **24 hours** without sleeping, the body builds up endogenous sleep inducing chemicals that increase the desire and ability to sleep.
    3) **Only Sleep for That Amount of Sleep Threshold Time**; after staying awake for 24 hours. The next night, the person should make sure that only sleep for the number of hours that determined to be minimum sleep threshold in step 1, (*for example*; if person wake up at 6:00am, and the minimum sleep threshold is 3 hours, then stay awake until 3:00 am before going to sleep).
    4) **Using Bright Lights to Help to Wake Up**; Bright light is the most powerful regulator of the sleep wake cycle. Using light will help reset a normal sleep/wake pattern. Using light for approximately ½ hour upon awakening is sufficient to regulate the sleep/wake cycle.
    5) **Gradually Increase Minimum Sleep Threshold**; after a week, the sleep threshold time should be increased in 15 to 30 minute every day or every other day, (*for example*, if person go to sleep at 3:00 am and get up at 6:00 am. The next night, he go to sleep at 2:45 am and get up again at 6:00 am). Still slowly increase sleep threshold to the point where are able to sleep for at least six hours a night and hopefully even a full eight hours.
    - **N.B.**; ***no* napping** and **no sleeping pills.**
- **Cognitive Therapy**; the patient is ***educated*** to correct inaccurate beliefs about sleep and to reduce catastrophic thinking and excessive worrying about the failing to obtain adequate sleep.
- **Relaxation Techniques**;
    - Relaxation techniques more effective in patients with high arousal levels, such as;
        1) **Progressive Muscle Relaxation**;
            - It is based upon the theory that an individual can learn to relax one muscle at a time until the entire body is relaxed. Beginning with the muscles in the face, the muscles are contracted gently for 1-2 sec. & then relaxed. This is repeated several times.
        2) **Biofeedback Relaxation**;
            - **Biofeedback**; is a technique that can help to gain more control over these normally involuntary functions, including migraine headaches, chronic pain, incontinence, and heart rate.
            - This method allows to observe biological signs such as heart rate and muscle tension by using biofeedback home device and shows how to adjust them by using different training, such as; deep breathing, alternately tightening and then relaxing different muscle groups.

### ➢ Cognitive Behavioural Therapy *VS* Medication Therapy:-

- **Sleep medications** can be an ***effective*** in **short-term treatment.**
- **Cognitive behavioural therapy** is a ***good treatment choice*** in **long-term sleep problems.**

## Pharmacological Therapy

- **Pharmacotherapy** is indicated ***for all forms*** of **insomnia** as long as it is part of an overall plan to deal with the causes and is used for well-defined periods. It ***should be*** considered **adjunctive therapy** only for ***short-term*** or chronic insomnia.
- There are several classes of **sedative-hypnotics** (*next topic*):
    - **Barbiturates**; which are ***no longer*** indicated;
    - **Non-barbiturates**; e.g., **Chloral Hydrate** (limited indications).
    - **Benzodiazepines**; which are widely used sedative-hypnotics.
    - **Non-benzodiazepines**; e.g., **Zolpidem**, **Zaleplon**, **Zopiclone** and **Eszopiclone**.
    - **Serotonin Agonists**; **Buspirone** is a partial agonist on $5\text{-HT}_{1A}$ receptors.
    - **Melatonin Agonists**; **Ramelteon** is a melatonin receptor 1 and 2 agonist.
    - **Orexin Antagonists**; **Suvorexant**; is an orexin receptor antagonist.
    - **First Generation Antihistamines**; e.g., **Doxylamine**.
    - **Antidepressants**; e.g., **Doxepin**.
    - **Herbal Agents**; e.g., **Valerian** and **Kava-Kava**.

# Sedative-Hypnotic Drugs

- **Anxiety**; is an ***unpleasant state*** of **tension**, **apprehension** or **uneasiness**.
- The ***physical symptoms*** of severe anxiety are similar to those of fear (***such as*** tachycardia, sweating, trembling and palpitations) and involve **sympathetic activation**.
- ***Severe*** **chronic anxiety** may be treated with **antianxiety drugs** (or anxiolytics) and/or some form of **psychotherapy** (cognitive behavioural therapy).
- *Because* many **antianxiety drugs** also ***cause some*** **sedation**, they may be used clinically as both **anxiolytic** and **hypnotic** (sleep-inducing).

## I) Benzodiazepines (BDZs)

➢ **Classification and *examples*:-**

| Long-acting (> 24 hrs. half-life) | | |
|---|---|---|
| **Diazepam** (Valium®) | **Clonazepam** (Rivotril®) | **Clorazepate** (Tranxene®) |
| **Quazepam** (Doral®) | **Flurazepam** (Dalmane®) | **Clobazam** (Frisium®) |
| Intermediate-acting (12-24 hrs. half-life) | | |
| **Bromazepam** (Calmepam®) | **Lorazepam** (Ativan®) | **Estazolam** (ProSom®) |
| **Chlordiazepoxide** (librium®) | **Temazepam** (Restoril®) | |
| Short-acting (< 12 hrs. half-life) | | |
| **Alprazolam** (Xanax®) | **Midazolam** (Dormicum®) | **Oxazepam** (Comedormir®) |
| **Triazolam** (Halcion®) | | |

- **Benzodiazepines** (**BDZs**) (*sometimes called* "**Benzos**") are originally developed in the 1960s to treat anxiety. *Now* these drugs are widely used anxiolytic drugs.
- BDZs; a class of ***psychoactive drugs***, ***chemical structure***; fusion of a **benzene** ring & **diazepine** ring.
- These drugs modulate the effects of the neurotransmitter gamma-aminobutyric acid (GABA).
- They have ***largely replaced*** **barbiturates** in the ***treatment*** of **anxiety** and **insomnia**, because benzodiazepines are ***generally*** *considered* to be **safer** and **more effective** ***but*** they are ***not necessarily*** the **best choice** for **anxiety** or **insomnia**. *Non*-**benzodiazepine hypnotics** and **antihistamines** may be ***preferable*** for **insomnia**.
- **Diazepam** [dye-AZ-e-pam], **Clonazepam** [kloe-NAZ-e-pam], **Clorazepate** [klor-AZ-e-pate], **Quazepam** [QUAY-ze-pam], **Flurazepam** [flure-AZ-e-pam] and **Clobazam** [KLOH-bah-zam] are long acting (> 24 hrs. half-life).
- **Bromazepam** [bro-MAZ-e-pam], **Lorazepam** [lor-AZ-e-pam], **Estazolam** [eh-STAY-zoe-lam], **Chlordiazepoxide** [klor-di-az-e-POX-ide] and **Temazepam** [te-MAZ-e-pam] are intermediate-acting (12-24 hrs. half-life).
- **Alprazolam** [al-PRAY-zoe-lam], **Midazolam** [mi-DAY-zoe-lam], **Oxazepam** [ox-AZ-e-pam] and **Triazolam** [try-AY-zoe-lam] are short-acting (< 12 hrs. half-life).

** ***All*** **benzodiazepines** are **sedating** (***anxiolytic***), ***but*** only ***five*** benzodiazepines are FDA approved as **sedative-hypnotics** *because* they are rapidly absorbed and produce CNS sedation more quickly;

**5 BDZs Hypnotics**

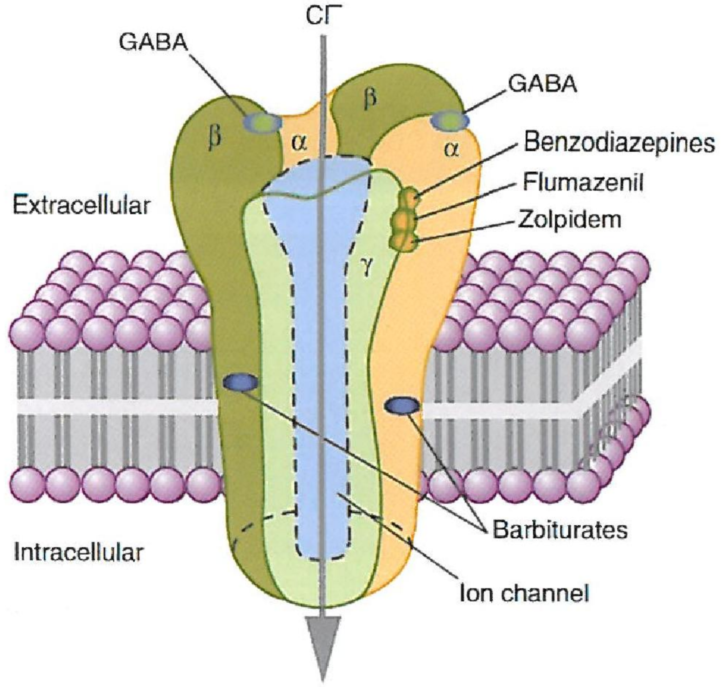
- ***Long-acting***; **Quazepam** and **Flurazepam**.
- ***Intermediate-acting***; **Temazepam** and **Estazolam**. - ***Short-acting***; **Triazolam**.

**Pharmaco Kinetics**

- **BDZs** are **lipophilic**, after oral administration they are ***rapidly*** and ***completely*** **absorbed**.
- **BDZs** are distribute throughout the body and ***penetrate*** into the **CNS**.
- ***All*** **sedative-hypnotics** ***cross*** the **placental barrier** ***during*** **pregnancy**.
- **Sedative-hypnotics** are also ***detectable*** in **breast milk**.
- The **half-lives** of the BDZs are ***important*** clinically, ***because*** the **duration of action** may ***determine*** the **therapeutic usefulness**. The longer-acting agents form active metabolites with long half-lives.
- ***Most*** BDZs undergo **hepatic microsomal system** and **renal *clearance***.

## Mechanism OF Action

- The ***targets*** for **BDZs** actions are the **GABA$_A$ receptors.**
- **GABA$_A$** receptor, functions as a Cl$^-$ channel, is activated by GABA.
- **BDZs**, **Barbiturates**, **Zolpidem**, **Zaleplon**, **Eszopiclone** and ***many*** **other drugs** ***bind*** to **receptor sites** ***on the*** **GABA$_A$ receptor** in CNS.
- A major ***isoform*** of the **GABA$_A$ receptor** that is found in many regions of the brain consists of **two $\alpha_1$**, **two $\beta_2$**, and **one $\gamma_2$ subunits**.



- *In this isoform*, the **two binding sites** *for* **GABA** are located between $\alpha_1$ and $\beta_2$ subunits and the **BDZs binding sites** (BZ site) is between an α and γ subunit, so ***selectivity*** of **sedative-hypnotics drugs** ***depending on*** **GABA$_A$ receptor isoform**, i.e. **Barbiturates** (*non-selective*) also bind to multiple isoforms of the GABA$_A$, **BDZs** (*selective*) also bind to GABA$_A$ receptor isoforms that contain α and γ subunit, while **Zolpidem**, **Zaleplon** and **Eszopiclone** (*more selective*) bind more selectively because these drugs interact only with GABA$_A$ receptor isoforms that contain **$\alpha_1$** subunits.
- In contrast to GABA itself, benzodiazepines and other sedative-hypnotics have a low affinity for GABA$_B$ receptors.
- ***BDZs Mechanism of Action***;
  1) **BDZs** ***potentiate*** the **action** *of* **GABA** by binding to BDZs sites (BZ$_1$ or BZ$_2$) on GABA$_A$ receptors ⇨ ***increasing*** their **affinity** *for* **GABA**.
  2) This ***results*** in an ***increased*** **opening** of **Cl$^-$ channels** and ***enhanced*** **hyperpolarization** ⇨ sedative effect.

***Based on studies***; it has been suggested that **$\alpha_1$** subunits in GABA$_A$ receptors mediate ***sedation***, ***amnesia***, and ***ataxic effects*** of benzodiazepines, whereas **$\alpha_2$** and **$\alpha_3$** subunits are involved in their ***anxiolytic*** and ***muscle-relaxing actions***.

## Pharmacological Action

- ***All*** **BDZs** ***exhibit five therapeutic*** **properties**;
  1) **Anxiolytic** (*also known as* **minor tranquilizers**);
     - ***At low doses***, ***all*** **BDZs** are **anxiolytic**; by selectively ***enhancing*** **GABAergic transmission** in neurons having **GABA$_A$ receptors** with **$\alpha_2$ subunit** ⇨ ***inhibiting*** neuronal circuits in the limbic system of the brain.
  2) **Hypnotic**;
     - ***At high doses***, all benzodiazepines have hypnotic effects.
     - The hypnotic effects are mediated by the **$\alpha_1$-GABA$_A$** receptors.
     - ***Only*** five BDZs are **FDA approved** as **sedative-hypnotics**.
  3) **Amnesic Actions** (*memory loss*);
     - ***All*** **BDZs** cause ***temporary*** **impairment of memory**, it is also mediated by the **$\alpha_1$-GABA$_A$** receptors.

## Pharmacological Action

**4) Anticonvulsant**;

- ***Several*** **BDZs** have **anticonvulsant activity.**
- This effect is ***partially***, mediated by **$\alpha_1$-GABA$_A$** receptors.

**5) Muscle Relaxant**;

- ***At high doses***, ***several*** **BDZs** ***relax*** the ***spastic*** **skeletal muscle**, by acting on GABA receptors in the spinal cord.

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## Therapeutic Uses

- The benzodiazepines show differences in their relative anxiolytic, anticonvulsant, and sedative properties. Duration of action and pharmacokinetic are important in choosing one BDZ over another.

**1) Anxiety Disorders**;

- **BDZs** are ***effective*** for the treatment of the **anxiety disorders**, such as panic disorder, generalized anxiety disorder (GAD), obsessive compulsive disorder and extreme anxiety associated with phobias, such as flying.
- **BDZs** for the ***treatment*** of **anxiety** is ***based on*** **several pharmacologic principles**:
    1) Rapid onset of action.
    2) Relative high therapeutic index.
    3) Low risk of drug interactions.
    4) Minimal effects on CV or autonomic functions.

* Newer antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), are now considered to be drugs of ***first choice*** in anxiety disorders (see page no. 294).

- ***The most commonly prescribed BDZs as anxiolytic***; **Clonazepam**, **Chlordiazepoxide**, **Lorazepam**, **Diazepam** and **Alprazolam**.

**2) Sleep Disorders**;

* **Non-pharmacologic therapies** are ***useful*** and ***safer*** for sleep disorders.

* If patient will need and should be given a sedative-hypnotic, It ***should be*** for a ***limited period***.

* It should be ***gradually discontinue***, it can lead to **rebound insomnia**.

- **BDZs** can cause a ***dose-dependent*** **change in sleep patterns**;
    1) Decrease in rapid eye movement (REM) sleep stage.
    2) Decrease in slow-wave sleep stage.
    3) Increase in stage 2 non-rapid eye movement (NREM).
- The ***newer hypnotics***; **Zolpidem**, **Zaleplon** and **Eszopiclone** are less likely than the BDZs to change sleep patterns.
- ***The most commonly prescribed BDZs as sedative-hypnotics***; **Quazepam**, **Flurazepam**, **Temazepam**, **Estazolam** and **Triazolam**.

* People with **problems** in ***sleep initiation***; most likely benefit from an agent with a quick onset.

* People with **problems** in ***sleep maintenance***; most likely benefit from an agent with a longer half-life.

- ***N.B.***;
    - **Triazolam** (***short acting***) is a more frequently to develop tolerance ***within*** a **few days**, ***so*** it is ***not*** a **preferred agent** and it is best to ***used it*** **intermittently**.
    - The use of sedative-hypnotics for ***more than*** **1-2 weeks** leads to some **tolerance** to their effects on sleep patterns.

## Therapeutic Uses

**3) Adjuncts to Anesthesia;**

- The ***shorter-acting agents*** (**Midazolam**) are often ***used to*** **facilitate amnesia** in anxiety-provoking procedures, such as endoscopy, dental procedures and angioplasty.
- **Diazepam**, **Lorazepam** & **Midazolam** are used *IV* in **anesthesia.**

**4) Seizures;**

- In a **hospital emergencies; IV Clonazepam** (*stronger*), **Lorazepam** (*longer*) and **Diazepam** (*faster*) are ***first-line choices.***
- **Clobazam** is ***widely used*** by ***specialist*** **epilepsy clinics** ***worldwide***, while **Clonazepam** is ***most*** **popular.**

**5) Alcohol Withdrawal Syndrome;**

- **Chlordiazepoxide** (*most commonly*), **Clorazepate**, **Diazepam**, **Lorazepam**, and **Oxazepam** are the ***preferred choice*** to ***reduce*** the **risk** of **withdrawal-related seizures.**

**6) Muscle Spasms;**

- **Diazepam** is ***useful*** in the treatment of skeletal muscle spasms.
- **Baclofen** or **Tizanidine** are sometimes used as an alternative to benzodiazepines (see page no. 406).

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## Side Effects

- *Next day* **drowsiness** and **confusion** (*most common side effects*);
    - ***Most*** common with ***long-acting as*** **Diazepam** & **Flurazepam.**
- *Next day* **sedation**, **ataxia** and **impair driving**;
    - ***Most*** common in elderly.
- *Cognitive Impairment* (**Anterograde Amnesia**);
    - ***All*** BDZs with ***long-term*** **use** appear to ***impair ability*** to learn new information and may also impair memory storage and recall.
- **Hypotension** & **Respiratory Depression**;
    - **IV** BDZs can be associated with cardiac and/or respiratory arrest.
- **Rebound Insomnia**;
    - Can occur when the drug is discontinued abruptly and usually lasts for 1-2 days It is most common after the use of short acting agents (*most common with*; **Triazolam**).
- **Tolerance**, **Dependence** and **Abuse**;

**** Tolerance ****

- ***Tolerance***; decreased responsiveness to the usual doses of the drug.
- It is occurs when used for more than **1-2 weeks**.
- It is ***associated with*** a decrease in **GABA receptor density**.
- ***Cross-tolerance*** exists between the **BDZs** and **Ethanol**.
- **Triazolam** often shows a ***rapid development*** of tolerance.

**** Dependence** and **Abuse ****

- Psychological and physical dependence on BDZs can develop if high doses of the drugs are given for a prolonged period.
- Dependence occurs within weeks to months of continued use.
- ***Abrupt*** **cessation** can ***lead to*** *withdrawal symptoms*; **Confusion, anxiety, agitation, restlessness, insomnia, tension** and (*rarely*) **seizures.**
- ***Short-acting*** **BDZs**, such as **Triazolam**, induce more abrupt and ***severe*** **withdrawal reactions.**

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## Notes

- **Sedative-hypnotics** may ***increase*** the **risk** of **fetal malformations** if used during the first trimester.
- **Alcohol** & *other* **CNS depressants** ↑ sedative–hypnotic effects of BDZs.
- ***Most*** **sedative-hypnotics** are ***contraindicated*** or ***used with caution*** in patients with **renal** or **hepatic disease.**
- **BDZs** should be ***avoided*** in patients with acute **closed-angle glaucoma.**
- **BDZs** are considerably ***less*** **dangerous** than the older anxiolytic-hypnotics.
- **Flumazenil** (BDZs antagonist) used in BDZs overdoses (***see next page***).

### Flumazenil (Anexate®)

- **Flumazenil** [floo-MAZ-eh-nill] ***rapidly reverses*** the **effects of BDZs** by ***competitive*** **inhibition** at the **BDZs binding site** on the **GABA$_A$ receptor**.
- It is primarily ***used*** to treat **benzodiazepine overdoses**.
- The drug is available for **IV administration *only***.
- ***Onset*** is ***rapid*** (within one to two min.), ***but*** the ***duration*** is ***short***, with a half-life of about 1 hour, so, ***frequent administration*** may be **necessary** to ***maintain*** **reversal** of a **long-acting BDZs**.
- ***Dose***; 0.2 mg IV one time over 30 seconds ⇨ if no response after 30 seconds ⇨ repeated 0.5 mg every minute (maximum 3 mg/hr).
- ***Common side effects***; dizziness, nausea, vomiting and agitation.

## II) Barbiturates

- The ***first*** barbiturate drug, **Barbital**, was synthesized in 1902, by 1904, several related drugs derived from **barbituric acid**, including **Phenobarbital**, had been synthesized.
- **Phenobarbital** was brought to market in 1912 by the drug company Bayer as the brand Luminal®.
- **Barbiturates** are ***nonselective*** **CNS depressants**.
- **Barbiturates**, were be used as **anxiolytic-hypnotic** ***in the past***, but **today** they have been ***largely replaced*** by the **benzodiazepines**, ***because***;

***BDZs are***

1) High therapeutic index.
2) More selective.
3) Mild physical dependence and tolerance.
4) Little cardiovascular and respiratory depression.
5) Not significantly enzyme inducer.
6) Available of specific antidote (**Flumazenil**).

➢ **Classification and *examples*:-**

| | | |
|---|---|---|
| Long-acting | | |
| **Phenobarbital** or **Phenobarbitone** (Luminal®) | | |
| Intermediate-short-acting | | |
| **Secobarbital** (Seconal®) | **Amobarbital** (Amytal®) | **Butalbital** (Fioricet®) |
| Ultra-short-acting | | |
| **Thiopental** (Pentothal®) | | |

- **Phenobarbital** [fee-noe-BAR-bital] has a **duration of action *greater than*** a **day (1-2 days)**.
- **Secobarbital** [see-koe-BAR-bi-tal], **Amobarbital** [am-oh-BAR-bi-tal] and **Butalbital** [bu-TAL-bi-tal] have a **duration of action *less than*** a **day (3-8 hours)**.
- **Thiopental** [thye-oh-PEN-tal] ***acts within*** **seconds** and has a ***duration of action*** of about **20 min**.

**Pharmaco Kinetics**

- ***After*** **oral** (**rectal** or **injection**) **administration**, **absorption** is usually ***rapid*** and ***relatively*** **complete**.
- The **sodium salts** are ***rapid*** **dissolution** and are **absorbed *more quickly***.
- Once absorbed the barbiturates are rapidly **distributed *to all tissues*** and **fluids**.
- Barbiturates readily ***cross*** the **placenta** and are ***excreted*** into **breast milk**.
- Barbiturates generally are ***slowly*** **metabolized** and/or **conjugated** in the liver and then ***excreted*** renally (***Alkalinization*** of **urine ↑ elimination**).

**Mechanism OF Action**

- **Barbiturates *enhances* GABAergic transmission** by ***binding*** to the **site of barbiturates** on the **GABA$_A$ receptors** ⇨ ***prolonging*** the **duration of the $Cl^-$ channel openings** ⇨ **sedative-hypnotic *action***.
- **Barbiturates** ***can block*** **excitatory glutamate receptors**.

## Pharmacological Action

1) **CNS Depression**;
   - *At low doses*; **Sedation.**
   - *At normal doses*; **Anxiolytic** and **anticonvulsant effects.**
   - *At higher doses*; **Hypnosis**, ***followed by*** (depending on the dose) **anesthesia** and finally **coma** and **death.**

2) **CVS Depression**;
   - *At low doses*; Minimal effects.
   - *At higher doses*; **Hypotension** ***due to*** inhibition of ganglionic transmission and depression of vasomotor center (VMC).

3) **Respiratory Depression**;
   - *Lethal doses*; **Respiratory depression** and **death** due to ***depression*** in **respiratory center** (RC) in CNS.
   - *The Lethal Injection*; **Barbiturates** are the ***main component*** of the **lethal injection**; such as ultra-short acting (**Sodium Thiopental**), as an **anesthetic** agent (unconscious in less than 30 seconds) and *facilitate* **respiratory depression.**

4) **Liver Microsomal Enzyme Inducers**;
   - **Barbiturates** ***induce*** a **number of hepatic CYP enzymes** (most notably CYP2C9, CYP2C19 and CYP3A4), leading to **1)** ***exaggerated effects*** from many **pro-drugs** and **2)** ***decreased effects*** from **drugs** *which are* **metabolized** *by* **these enzymes.**

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## Therapeutic Uses

1) **Anesthesia**;
   - The ultra-short-acting barbiturates (**Thiopental**), have been used IV to **induce anesthesia** but have largely been replaced by other agents.

2) **Sedative-hypnotic**;
   - **Barbiturates** were ***used as*** sedatives to relieve anxiety, but ***now*** **rarely** (or not) used.
   - **Butalbital** is ***commonly*** **used** in ***combination with*** acetaminophen and caffeine or aspirin and caffeine as a sedative to assist in the management of **tension-headache** or **migraine headache.**

3) **Seizures**;
   - **Phenobarbital** has ***specific*** **anticonvulsant activity.**
   - It is the ***first-line choice*** for the treatment of **neonatal seizures.**
   - It is used in ***long-term*** management of **tonic-clonic seizures.**

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## Side Effects

- **Drowsiness**, **confusion** and **impaired concentration** (most common).
- The ***CNS depressant effects*** of **barbiturates** ***synergize*** with ***other*** **CNS depressant agents.**
- **Hypersensitivity**: facial edema and skin rash (1 to 2%).
- **Death** may also result from overdose (CV and respiratory depression).
- *Withdrawal Symptoms*; withdrawal is ***much more severe*** than that associated with opiates and ***can result*** in **death**. ***Abrupt cessation*** of barbiturates after chronic administration may cause tremors, anxiety, nausea, vomiting, seizures and cardiac arrest. ***Treatment of phenobarbital overdose*** is **supportive** (***no*** **antidote available**).
- **Tolerance**, **psychological** and **physical dependence** may occur with continued use.

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- *Drug Interactions*; ***Chronic*** barbiturate administration ***diminishes*** the action of many drugs that are metabolized by the CYP450 system (such as; phenytoin, oral contraceptives and most oral anticoagulants).
- **Barbiturates** *contraindicated* in **pregnancy**, it can depress the fetus.

# III) Other Agents

## Non-Barbiturates

### Chloral Hydrate (Chloral®)

- **Chloral Hydrate** [KLOR-uhl HYE-drate] is a **non-barbiturate sedative-hypnotic**.
- It was discovered through the chlorination (halogenation) of ethanol in 1832.
- Chloral hydrate has not been approved by the FDA and is on the list of unapproved drugs that are still prescribed by clinicians.
- **Hypnotic effects** of chloral hydrate due to its ***active metabolite*** **Trichloroethanol**.
- *Onset of Action*; 30-60 minutes.
- ***Plasma Half-life***; Trichloroethanol; 7-11 hours.
- ***Mechanism of Action***; not known.
- ***Uses***;
    - **Short-term insomnia**, it is also still used as a ***sedative prior*** to electroencephalography (EEG).
    - **Prevention of alcohol withdrawal symptoms**.
    - **Relieve anxiety *due to* certain procedures** (minor medical or dental).
- *Dose*; **Adult**; 500 mg to 1 g 15 to 30 min before bedtime [every 6 h, if needed (max, 2 g/day)].
  **Child**; 50 mg/ kg of body weight.
- ***Most Common Side Effects***; **Ataxia**; **dizziness**, **rashes** and **gastric discomfort**.

## Non-Benzodiazepines

### Zolpidem (Stilnox®)
### Zaleplon (Siesta®)
### Eszopiclone (Lunesta®)
### Zopiclone (Hypnor®)

- **Zolpidem** [ZOL-pi-dem], **Zaleplon** [ZAL-e-plon], **Eszopiclone** [es-ZOE-pi-clone] and **Zopiclone** [ZOE-pi-clone] are an ***oral*** **non-benzodiazepine hypnotics**, are also known as **Z-drugs** (***most*** of names start with the letter "Z").
- **Eszopiclone** is the active ***dextrorotatory*** stereoisomer of **Zopiclone**
- ***Mechanism of Action***; are ***agonists*** at the **$GABA_A$ $\alpha_1$ subunit**, by ***selectively*** binds to the **BDZs binding site *subtype* $BZ_1$**.
- ***Compared with BDZs***;
    - ***More*** selective as hypnotics agent.
    - ***Lower*** risk of tolerance and withdrawal.
    - ***No*** significantly alter the various sleep stages
    - ***No*** **anticonvulsant** or **muscle-relaxing** properties.
    - ***No*** respiratory depressant effect.
- ***Pharmacokinetics***;
    - After **oral administration** they are ***rapidly*** absorbed from the **GIT**.
    - ***Onset of action*** and ***duration of action***;

| | Onset of action | Duration of action |
|---|---|---|
| **Zolpidem** | 30 minuets | 5 hours |
| **Zaleplon** | 30 minuets | 3 hours |
| **Zopiclone** | 30 minuets | 5 hours |
| **Eszopiclone** | 20 minuets | 7 hours |

    - **Zolpidem** is available as an immediate release tablet (IR), controlled release tablet (CR), sublingual tablet (Edluar®) and sublingual spray (Zolpimist®), the FDA has ***reduced*** the **dosing** to ***limit*** **next day impairment**.
    - **Zaleplon** is indicated only for short-term treatment of insomnia (*duration*; 3 h.).
    - ***Metabolism***; They are metabolized, mainly by CYP450 isoform CYP3A4.
- ***Uses***; **insomnia treatment**; - **Zaleplon** is ***indicated only*** for **short-term treatment of insomnia**.
  - **Zolpidem** (SR) and **Eszopiclone** can be used for **chronic insomnia**.
- ***Side Effects***; **Nightmares**, **agitation**, **anterograde amnesia**, **headache** and **daytime drowsiness**.
- This drugs are classified as a Schedule IV controlled substance by federal U.S. drug policy.

# Serotonin Agonists

## **Buspirone** (Buspar®)

- **Buspirone** [byoo-SPYE-rone] is a ***selective*** **$5\text{-HT}_{1A}$ agonist**, which is an **antianxiety agent**.
- It is primarily ***used*** to treat **generalized anxiety disorder (GAD)**;
  - Good when BDZs should be avoided (e.g. in patients with a history of substance abuse); takes 2-4 weeks to be effective.
- *Contraindication*: should ***not*** be used with patient taking **MAOIs** may cause **serotonin syndrome**.
- ***Most common*** *side effects*: dizziness, nausea, headache, nervousness, and excitement.
- ***Usual*** **adult** *dose*:
  - **Initial dose**: 5 mg 3 times a day.
  - **Maintenance dose**: 20 to 60 mg/day in divided doses.
  - **Maximum dose**: 60 mg per day.
- **Buspirone** has shown ***no*** potential for **abuse** and ***no*** evidence of dependence or withdrawal effects has been observed.

# Melatonin Agonists

## **Ramelteon** (Rozerem®)

- **Ramelteon** [ram-EL-tee-on] is ***first*** in a **new class** of sleep agents that ***selective*** **agonist** at the **$MT_1$** and **$MT_2$** subtypes of **melatonin receptors** in the **suprachiasmatic nucleus** (SCN) [Melatonin is a hormone secreted by the pineal gland that helps to maintain the circadian rhythm underlying the normal sleep-wake cycle].
- ***Duration of Action***; 2-5 hours.
- ***Metabolism***; primarily by CYP 1A2, ***but*** affect by 2C9 and 3A4 inducers or inhibitors.
- **Ramelteon** ***used*** for ***long term*** for **chronic insomnia**, ***particularly*** in **patients *with* difficulty** in **sleep initiation**.
- ***Dose***; 8 mg orally within 30 minutes of going to bed. (Maximum dose: 8 mg per day).
- ***Common Side Effects***; dizziness, fatigue, somnolence and may also increase prolactin levels.
- ***To date***; it has ***minimal*** potential for abuse, and ***no*** evidence of dependence or withdrawal effects has been observed.

# Orexin Antagonists

- **Orexin (Hypocretin)** is a neuropeptide that regulates **arousal**, **wakefulness** and **appetite**.

## **Suvorexant** (Belsomra®)

- **Suvorexant** [SOO-voe-REX-ant] is a selective, dual orexin receptor antagonist ($OX_1$ and $OX_2$).
- It was approved by the FDA on 2014 and became available in US in February 2015.
- ***Uses***; **Insomnia**, ***characterized by*** **difficulties** with **sleep initiation** and/or **sleep maintenance**.
- It should be taken within 30 minutes of bedtime, and with at least 7 hours of sleep time.
- It is ***metabolized*** by CYP 3A4 (affect by 3A4 inducers or inhibitors).
- This drug is ***classified as*** a Schedule IV controlled substance by federal U.S. drug policy.

# Antihistamines

## **Doxylamine** (Donormyl®)

- **OTC** ***First*** **generation antihistamines** with ***sedating properties***, such as **Doxylamine** and **Diphenhydramine** are effective in ***treating*** **mild types** of **situational insomnia**, ***but not*** as effective as BDZs or non-BDZs.
- ***Side effects***; **anticholinergic effects**.

# Antidepressants

## **Doxepin** (Silenor®)

- **Doxepin** [DOX-e-pin] is an older **tricyclic antidepressant**.
- It was recently ***approved*** at **low doses** for the **management of insomnia**, ***particularly*** in **patients *with* difficulty sleep maintenance**.
- Other antidepressants, such as **Trazodone**, **Mirtazapine**, and other older tricyclic antidepressants with strong antihistamine properties are used ***off-label*** for the treatment of insomnia (see page no.297)

# Herbal Agents

## Valerian flower extracts

- *Because* of valerian's historical use as a sedative, antiseptic, anticonvulsant, migraine treatment, and pain reliever, most basic science research has been directed at the interaction of valerian constituents with the GABA receptor.
- Valerian is most often used as an alternative medicine for insomnia in place of hypnotic drugs. It is also sometimes used as an alternative for sedatives, in the treatment of certain anxiety disorders.
- ***Common side effects***; dizziness or drowsiness.

## Kava-Kava

- Kava or kava-kava (***Piper methysticum***) is renowned for its many health benefits, but the chiefly among them is its anxiolytic properties.
- The effect of kava as **anxiolytic-hypnotic**, ***duo to*** it acts on GABA receptor and it also inhibit the reuptake of norepinephrine and dopamine.
- It is also used for attention deficit-hyperactivity disorder (ADHD), psychosis, depression and others.

## *Humulus lupulus* (hops) extract

- One of the most widely known and studied medicinal properties of hops is its ability to induce sleep.
- Research has been found the sedative activity due to action on melatonin receptor or GABA receptor.

## II) Selective Serotonin Reuptake Inhibitors (SSRIs)

- **SSRIs** ***selectively inhibit*** the **reuptake** of **serotonin** into the presynaptic neuron (300-3000-fold greater selectivity for the serotonin transporter, as compared to the norepinephrine transporter).
- ***Advantage***; SSRIs have ***little*** blocking activity at muscarinic, α-adrenergic, and histaminic $H_1$ receptors. ***Therefore***, common side effects associated with TCAs, are not commonly seen with the SSRIs. ***Therefore*** **SSRIs** have ***largely replaced*** **TCAs** and as the ***drugs of choice*** in depression.
- The **FDA** has ***approved*** **six SSRIs** for the treatment of **depression**:

| | | |
|---|---|---|
| **Fluoxetine** (Prozac®) | **Sertraline** (Lustral®) | **Paroxetine** (Seroxat®) |
| **Fluvoxamine** (Faverin®) | **Citalopram** (Cipram®) | **Escitalopram** (Cipralex®) |

- **Fluoxetine** [floo-OX-e-teen] (the prototypic drug), **Sertraline** [SER-tra-leen], **Paroxetine** [pa-ROX-e-teen], **Fluvoxamine** [floo-VOX-e-meen], **Citalopram** [sye-TAL-oh-pram] and **Escitalopram** [es-sye-TAL-ohpram]. **Escitalopram** is the ***pure*** **S-enantiomer** of **Citalopram**.
- **Fluvoxamine** is ***indicated only*** for **obsessive-compulsive disorder** (**OCD**) but is an ***effective*** antidepressant. (**OCD**; ***see anxiety disorders***).

**Pharmaco Kinetics**

- ***All*** **SSRIs** are ***well*** **absorbed** after ***oral*** **administration**.
- **Food** has ***little*** **effect** on absorption (***except***, **Sertraline**; **↑ absorption**).
- **Fluoxetine** ***differs*** from the ***other*** **SSRIs**; It having a ***much*** **longer half-life**, ***due to*** it **active metabolite Norfluoxetine**, The ***elimination*** **half-life** of **Norfluoxetine** is about ***three*** **times** longer than **fluoxetine**. **Fluoxetine** has to be ***discontinued*** **4 weeks** or **longer** ***before*** an **MAOI** can be administered to ***decrease*** the **risk** of **serotonin syndrome**.

| | Half-life | Active metabolite | Usual dose (mg/day) | Maximal daily dose (mg) |
|---|---|---|---|---|
| Fluoxetine | 1-4 days | **Norfluoxetine** | 20-60 | 80 |
| Sertraline | 26 hours | No | 50-200 | 200 |
| Paroxetine | 21 hours | No | 10-60 | 50-60 |
| Fluvoxamine | 15 hours | No | 50-300 | 300 |
| Citalopram | 32 hours | No | 20-40 | 40 |
| Escitalopram | 27-32 hours | No | 10-20 | 20 |

- ***Extended formulations***: **Fluoxetine 90 mg** can be taken ***once*** **weekly**.
- **Escitalopram** is the ***S-isomer*** of **Citalopram**. At a 10-mg dose, it is as effective as citalopram 20 mg.
- ***Metabolism*** by **cytochrome P450** enzymes;
  - **Fluoxetine** and **Paroxetine** are potent inhibitors of the CYP2D6.
  - **Fluvoxamine** is an inhibitor of CYP3A4.
  - **Citalopram**, **Escitalopram** & **Sertraline**; modest CYP interactions.

- ***Mechanism of Action***; The SSRIs ***block*** the **reuptake of serotonin**, leading to ***increased*** **concentrations** of the **neurotransmitter** in the **synaptic cleft**.
  - ***Blockade*** of **serotonin reuptake** ***leads*** to an **increase** in **serotonin** ***overall*** and may ***influence*** all **subtypes** of **serotonin receptors**.
- The ***efficacy*** of **SSRIs** is **equal** for **treatment** of **depression**.
- ***Onset & duration***; **SSRIs** (***Other*** **Antidepressants**), typically take at ***least*** **2 weeks** to ***produce*** **significant improvement** in **mood** and ***maximum*** benefit may require up to **12 weeks** or **more**.

**Therapeutic Uses**

- **Depression**; All SSRIs ***except*** **Fluvoxamine** (***but*** it is effective).
- **Generalized Anxiety Disorder** (**GAD**); All SSRIs ***except*** **Fluvoxamine**.
- **Obsessive Compulsive Disorder**; All SSRIs.
- **Eating Disorders** (**Bulimia Nervosa**); ***only***, **Fluoxetine**.
- **Stroke Recovery** All SSRIs ***except*** **Fluvoxamine**.
- **Premature Ejaculation**. All SSRIs (*include*; **Dapoxetine**) ***except*** **Fluvoxamine**.

## Side Effects

- **SSRIs** are considered to have ***fewer*** or ***less*** **severe adverse effects** than the **TCAs** and **MAOIs**, ***but not without*** **adverse effects**.
- ***In general***; **side effects of SSRI**; GI side effects (nausea, vomiting and diarrhea), headache, anxiety, agitation, fatigue, sexual dysfunction, changes in weight and sleep disturbances.
- **GI Side Effects**;
  - **SSRIs** ***enhance*** **serotonergic tone**, ***not*** just in the brain ***but*** **throughout the body**.
  - ***Increased*** **serotonergic activity** in the **gut** is commonly associated with nausea, GI upset, diarrhea, and other GI symptoms.
- **Sleep Disturbances**;
  - **Paroxetine** and **Fluvoxamine** are ***the most*** **sedating** SSRIs. May be useful in patients who have difficulty sleeping.
  - **Fluoxetine** and **Sertraline** are ***the most*** **activating** SSRIs, May be useful in patients who have excessive somnolence.
- **Sexual Dysfunction**;
  - Which may include loss of libido and delayed ejaculation.
  - ***Treatment of SSRI-induced sexual dysfunction***;
    1) Adding **Bupropion**, or
    2) Lowering the dose of the SSRI, or
    3) Adding an agent such as **Sildenafil** or **Cyproheptadine**, or
    4) Changing to a drug less likely to cause this problem.
- **Citalopram** 40 mg ***increase*** the **risk** of **QT interval** ***prolongation***.
- **SSRIs** appear to ***increase*** the **risk** of **bleeding.**

## Serotonin Syndrome

- Because these drugs have ***potent*** **serotonergic activity**, **combinations** with ***other drugs*** **affecting serotonin** can ***lead to*** **serotonin syndrome**.
- ***Other drug*** **examples**; MAOIs, TCAs, SNRIs, Dextromethorphan, Meperidine, Sympathomimetics, Triptans and Lithium.
- **Serotonin syndrome** ***includes***;
  1) **Neuromuscular hyperactivity**;
     - Muscle rigidity, tremors and incoordination.
  2) **Altered mental status**;
     - Agitation, confusion and hypomania.
  3) **Autonomic instability**;
     - Hyperthermia and diaphoresis.
- ***Treatments***;
  - ***Discontinuing*** the **offending agent**.
  - **Supportive treatments** *such as* **cooling blankets** and **respiratory assistance** and ***providing*** **Clonazepam** ***for*** **seizures** and **Nifedipine** ***for*** **hypertension**.

## Withdrawal Symptoms

- ***Sudden*** **discontinuation** of **short half-life** SSRIs such as **Paroxetine** and **Sertraline** is associated with a ***discontinuation syndrome*** in some patients ***characterized by***;
  - Dizziness, malaise, and flu-like symptoms, agitation and irritability, nervousness and changes in sleep pattern.
- Symptoms ***beginning*** 1 or 2 days after stopping the drug and persisting for 1 week or longer.
- ***So*** a ***gradual dose reduction*** (e.g., over 2-4 weeks) may be indicated.
- **Fluoxetine** has the lowest risk of causing an SSRI withdrawal syndrome.

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- ***Pregnancy***; ***Most*** **antidepressants** are **category C** (**Paroxetine** is a category D).
- ***Children***; Antidepressants should be used cautiously in children,
  - **Fluoxetine**, **Sertraline** and **Fluvoxamine** are approved for use in ***children*** to treat **obsessive-compulsive disorder**.
  - **Fluoxetine** and **Escitalopram** are approved to treat ***childhood*** **depression**.

## III) Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs)

- **SNRIs** ***inhibit*** the **reuptake** of **serotonin** and **norepinephrine** into the presynaptic neuron.
- ***Unlike*** **TCAs**, they have ***negligible*** *effects* at other receptors that cause anticholinergic or antihistaminic adverse effects, with the possible ***exception*** of **Duloxetine**, which appears to have a ***slightly*** **higher** incidence of **anticholinergic** symptoms.
- **SNRIs**, ***may be*** effective in **depression** in ***patients in whom*** **SSRIs** are ***ineffective***.
- **SNRIs**, ***may be*** effective in **depression** is often ***accompanied*** by ***chronic*** **painful symptoms**, such as **backache** and **muscle aches** (This pain is, in part, modulated by serotonin and norepinephrine pathways in the CNS).
- Both **SNRIs** and **TCAs**, are **effective** in relieving pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, fibromyalgia and low back pain.
- The **SNRIs** have ***relatively fewer*** **CYP450 interactions** ***than*** the **SSRIs**.
- ***All*** the **SNRIs** may ***produce*** **serotonin syndrome**.
- **SNRIs** ***may produce*** a **withdrawal syndrome** ***if*** treatment is ***abruptly*** **stopped**.
- ***Both*** **Duloxetine** and **Venlafaxine** have been ***associated*** with ***higher rates*** of **suicide** compared with **SSRIs**. The ***risk of*** **suicide** with **SNRIs** is ***still lower*** than with **TCAs**.

### Venlafaxine (Effexor®) | Desvenlafaxine (Pristiq®)

- **Venlafaxine** [VEN-la-fax-een] is a ***potent inhibitor*** of **serotonin** reuptake and at ***medium*** to ***higher*** **doses**, is an ***inhibitor*** of **norepinephrine** reuptake (at doses less than 150 mg/day, it has primarily a serotonin effect).
- **Desvenlafaxine** [dez-VEN-la-fax-een] is the active metabolite of **Venlafaxine**.
- **Venlafaxine** is a ***substrate*** but ***not*** an **inhibitor** of CYP2D6.
- **Desvenlafaxine** is a ***minor*** **substrate** for CYP3A4.
- ***Usual adult*** *dosage*; - **Venlafaxine** 75-375 mg/d. - **Desvenlafaxine** 50-200 mg/d.
- ***Side effects***; ***similar*** to that of the **SSRIs** (GI effects are common), they are ***can*** cause ***increases*** in blood pressure, which are ***usually*** **mild** and not clinically significant ***unless*** the patient already has **hypertension** that is ***not well*** **controlled**.

### Duloxetine (Cymbalta®)

- **Duloxetine** [doo-LOX-e-teen] is an ***inhibitor*** of **serotonin** and **norepinephrine** reuptake at ***all doses***.
- It is a ***moderate inhibitor*** of CYP2D6.
- It is ***indicated for*** the **treatment** of:
  1) **Major Depressive Disorder.**
  2) **Generalized Anxiety Disorder.**
  3) **Diabetic Peripheral Neuropathy.**
  4) **Fibromyalgia.**
  5) **Chronic Musculoskeletal Pain** ***caused by*** **chronic lower back pain** or **osteoarthritis pain.**
- ***Usual adult*** *dosage*; 40-120 mg/d.
- ***Side effects***; ***similar*** to that of the **SSRI**, ***increase*** **blood pressure**, **tachycardia** (*monitor* blood pressure), **dry mouth** and **constipation**.
- **Duloxetine** can ***cause*** **liver toxicity** ***and should not*** be **used in patients** with **hepatic insufficiency** and ***severe*** **renal impairment**.

### Levomilnacipran (Fetzima®)

- **Levomilnacipran** [leevo-mil-NA-si-pran] is a newly approved SNRI, It is the enantiomer of **Milnacipran** (an older SNRI).
- It is the ***most*** **noradrenergically** active of the SNRI class.
- It is ***primarily metabolized*** by CYP3A4.
- It is ***indicated*** for the ***treatment*** of **major depressive disorder** in adults. It is ***not approved*** for the **management of fibromyalgia**.
- ***Usual adult*** *dosage*; 40-120 mg/day.
- ***Side effects***; ***similar*** to that of the **SSRI**, ***increase*** **blood pressure**, **tachycardia** (*monitor* blood pressure) and **constipation**.

## IV) Norepinephrine Reuptake Inhibitors (NRIs)

### Reboxetine (Edronax®)

- **NRIs** ***are commonly*** used in the treatment of conditions like **ADHD** and **narcolepsy** due to their ***psychostimulant effects*** and in **obesity** due to their ***appetite suppressant effects***. They are also frequently used as ***antidepressants*** for the treatment of **major depressive disorder**, **anxiety** and **panic disorder**.
- **NRIs** ***may produce*** a **withdrawal syndrome** *if* treatment is ***abruptly*** **stopped**.
- **Reboxetine** is primarily ***metabolized*** by the CYP3A4 isozyme.
- **Reboxetine** is indicated for the ***treatment*** of **depression**.
- ***Most common*** **side effects** of **Reboxetine**; insomnia, nausea, sweating, dry mouth and constipation.
- *Contraindications*; **Reboxetine** is ***contraindicated*** in **narrow-angle glaucoma**, **cardiovascular disease**, **epilepsy**, **bipolar disorder**, **patients** ***concomitantly*** on **MAOIs**.
- *N.B.*; **Atomoxetine** (Strattera®) is another norepinephrine reuptake inhibitor ***approved*** for the **treatment** of **attention deficit hyperactivity disorder** (**ADHD**) (*see later*).

## V) Atypical Antidepressants

- The atypical antidepressants are a mixed group of agents that have actions at several different sites.
- Each drug in this category has a **unique mechanism** of action.

### Bupropion (Wellbutrin®)

- **Bupropion** [byoo-PROE-pee-on] is a ***weak*** **norepinephrine-dopamine** ***reuptake*** **inhibitor** (**NDRI**), the ***exact*** **mechanism** of action remains **unknown**.
- It is ***indicated*** for;

  - **Major depressive disorder** and **seasonal affective disorder**.
  - **Smoking cessation**; it ***reduces*** the **severity** of **nicotine withdrawal symptoms**, but ***somewhat less*** **effective** than **Varenicline** (Chantix®) (see page no. 42).
  - **Sexual dysfunction**; it is the ***drug of choice*** for the ***treatment*** of **SSRI-induced sexual dysfunction**.
  - **Attention Deficit Hyperactivity Disorder** (**ADHD**); It is not very common to use it.
  - **Obesity**; FDA approves **Bupropion/Naltrexone** (Contrave®).
- ***Usual adult*** ***dosage***; 200-450mg/day (in 2 or 3 divided doses).
- ***Most common*** **side effects**; ***increased*** **risk of seizures**, **insomnia**, **anxiety**, **irritability**, **headache**, and ***decreased*** **appetite**.
- *Warning*; **Bupropion** ***should not be*** **prescribed** to individuals with **epilepsy** or other conditions that ***lower*** the **seizure threshold**.
- The ***risk*** of **seizures** can be ***minimized*** by the following:
  1) Avoid use in susceptible patients (history of seizure disorder and eating disorders).
  2) Do not give more than 150 mg/dose or 450 mg/day.
  3) Avoid dosage titration any more frequently than every 3 days.

### Mirtazapine (Remeron®)

- **Mirtazapine** [mir-TAZ-a-peen] ***has*** a ***complex*** **pharmacology**;
  1) ***Block*** **presynaptic $\alpha_2$ receptors** ⇨ ***enhances*** the **release norepinephrine** and **serotonin**.
  2) ***Block*** **5-HT$_2$** and **5-HT$_3$** receptors.
  3) ***Potent*** **H$_1$ antagonist**.
- It ***not*** cause the ***antimuscarinic*** side effects like TCAs, or interfere with ***sexual function*** like SSRIs.
- It is ***used primarily*** in the **treatment** of **depression**. It is also ***off-label used*** as an **anxiolytic**, **hypnotic** and **appetite stimulant**.
- **Mirtazapine** may be an ***advantage*** in **depressed patients** ***having*** **difficulty sleeping**.
- ***Usual adult dosage***; 15-45/day.
- ***Most common*** **side effects**; ***Marked*** **sedation**, ***increased*** **appetite**, **weight gain** and **constipation**.
- **Mirtazapine** and **other antidepressants** may ***cause*** a **withdrawal syndrome** upon discontinuation.

# Augmentation Therapy

## ➢ Augmentation Therapy:-

- *Augmentation regimens include the following:*

1) **Lithium**; ***Adding*** lithium appears to ***help in*** **treatment-resistant depression**. ***The dosing*** ranging from full doses to small doses (*The drug discussed in bipolar disorder*).
2) **Thyroid**; ***Adding*** thyroid is also ***effective*** for **treatment-resistant depression**. Thyroid hormones thyroxine ($T_4$ and$T_3$) play an important role in cognitive function, mood, ability to concentrate, memory, attention span and emotions. ***The usual dose*** is 25 mcg/day.
3) **Buspirone**; has also been used as an augmenting agent.
4) **Second-generation antipsychotics** (**SGAs** or **atypical antipsychotics**) are also being used as adjuncts to antidepressant therapy. ***Almost*** all of them have been used, ***but*** only **Aripiprazole** and **Quetiapine** have FDA approval for **treatment-resistant depression**. **Olanzapine** in combination with **Fluoxetine** is also approved for **treatment-resistant depression**. (*This drugs discussed in Schizophrenia disorder*).
5) **Omega-3 fatty acids** and/or **Folate** and/or **Vitamin B**; may play a role in certain cases of depression.

# Combination Therapy

## ➢ Combination Therapy:-

- *Advantages*;
  - ***Overcome*** one or more **adverse effects** of ***another*** drug.
  - Use ***lower* doses** of each may ***lead to fewer*** **adverse effects**.
- *For example*;
  1) ***Adding*** **Trazodone** to **SSRI** therapy to ***treat*** **SSRI-induced insomnia**.
  2) ***Adding*** **Bupropion** to **SSRI** therapy for patients who ***do not fully*** **respond** to the **SSRI alone**.

# Electroconvulsive Therapy (ECT)

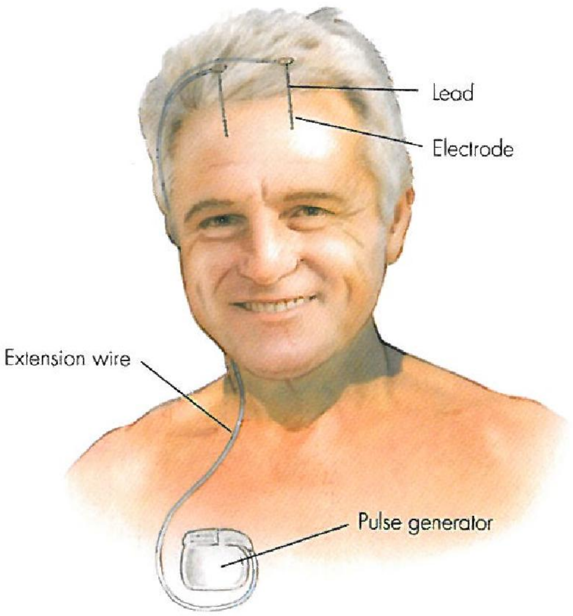
## ➢ Electroconvulsive Therapy (ECT):-

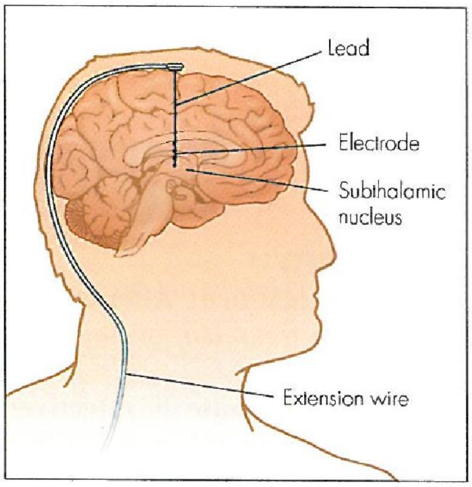
- **ECT** has the ***highest rates*** of **response** and **remission** of any ***form*** of **antidepressant treatment**, with **70-90%** of patients treated ***showing*** **improvement**.
- *Indication*: ***Option*** for **refractory depression**, **depression in pregnancy**, **psychotic depression**, and **drug-resistant depression**.
- *Treatments course* ***usually*** administered **two** or **three** ***times*** per **week**. An acute course of ECT typically consists of **6-12 treatments**, until symptoms have remitted or clearly reached a plateau.
- *Procedure*;
  - **ECT**; is a **procedure**, done under **general anesthesia**, in which ***small*** **electric currents** are passed through the brain.
  - The ***exact mechanism*** of ECT ***remains*** **elusive** (unknown).
  - ***CV side effects***; managed by optimizing blood pressure and monitor ECG during procedure.
  - **Confusion** that generally lasts 30-60 minutes after treatment.

# Medical Device Therapy

## ➢ Deep Brain Stimulation (DBS):-

- **DBS**; is a neurosurgical procedure introduced in 1987, ***implantation*** of a **medical device *called*** a **neurostimulator** or **brain pacemaker,** which ***sends*** **electrical impulses** to ***specific parts*** of the **brain** (*mechanism unknown*).


Lead
Electrode
Extension wire
Pulse generator

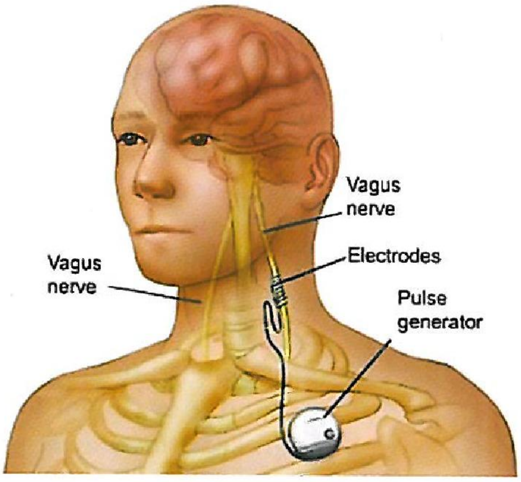

Lead
Electrode
Subthalamic nucleus
Extension wire

**Note:** Wire and electrodes are under the scalp

- It is ***used*** in ***treatment*-resistant movement** and **affective disorders *such as*** **Parkinson's disease, essential tremor, chronic pain, major depression** and **obsessive–compulsive disorder** (**OCD**).

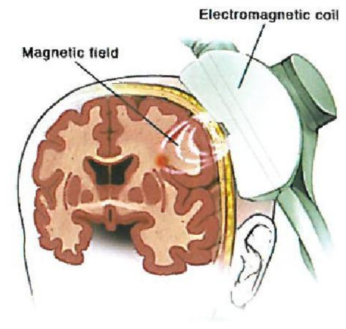
## ➢ Vagus Nerve Stimulation (VNS):-

- **VNS**; is a surgical procedure that can be used in **treatment-resistant depression**.
- **Pacemaker-*like device*** that is ***implanted*** in the body.
- The device is ***attached*** to a **stimulating wire** that is ***threaded*** along a **vagus nerve.**
- The **vagus nerve *travels up*** the neck to the brain where it connects to areas ***believed*** to be involved in **regulating mood.**
- ***Once implanted***, this device delivers regular electrical impulses to the **vagus nerve.**
- Uses an ***implanted*** electrode and generator to ***deliver*** **electrical pulses** to **vagus nerve.**


Vagus nerve
Electrodes
Pulse generator
Vagus nerve

## ➢ Transcranial Magnetic Stimulation (TMS):-

- **TMS**; is a ***non-invasive*** **procedure** that uses **magnetic fields** to ***stimulate*** **nerve cells** in the brain to ***improve*** **symptoms of depression**. TMS is typically used to treat **treatment-resistant depression.**


Electromagnetic coil
Magnetic field

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## ➢ Cranial Electrotherapy Stimulation (CES):-

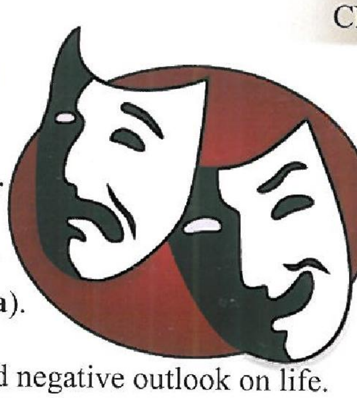
- **CES**; is a ***non-invasive*** **procedure** that applies a ***small, pulsed*** **electric current** across a person's **head** to ***treat*** **anxiety**, **depression**, **insomnia** and **chronic pain**.
- **Electrodes** are *placed* on the **ear lobes**.

# STAR*D Study

## ➢ STAR*D Study:-

- **Sequenced Treatment Alternatives to Relieve Depression** (STAR*D) was a collaborative **study** on the ***treatment*** of **depression**, funded in 2006 by the **National Institute of Mental Health**.
- Its ***designed*** to **evaluate** the **effectiveness** of a ***sequenced*** **approach to therapy**.
- ***Highlights*** of **STAR*D** ***include the following***;
  1) ***All*** **patients** were ***initially treated with*** **Citalopram** ***monotherapy***, and ***only*** about **30% achieved remission**.
  2) **Patients** who ***did not*** **achieve remission** were then allowed to select a **"switch" strategy** ***or*** **"augmentation" strategy (Level 2)**;
     - ***Options included*** **Bupropion**, **Sertraline**, **Venlafaxine** ***or*** **Cognitive therapy**.
     - There were no significant differences between strategies, but slightly higher remission rates occurred with augmentation.
     - **Bupropion** and **Buspirone** augmentation worked similarly.
  3) **Patients** ***not responding*** to **level 2** were then allowed to change to **Mirtazapine** or **Nortriptyline** ***or*** to have ***augmentation with*** **Lithium** or **Thyroid**;
     - There were not many differences between strategies.
     - Thyroid augmentation worked as well as lithium.
- ***Results***;
  - **Remission rates** ***decreased*** at **each level** of **treatment**.
  - **The results** ***suggest*** that ***less than*** **1/3 of patients** ***achieve*** **remission** with ***initial*** **SSRI monotherapy**.
  - **Switching** or **augmentation strategies** are ***viable*** **options**, with ***no*** **marked** ***increase*** in **efficacy** with **either strategy**.
  - **Switching antidepressants**; ***may be*** a **good option** for **patients** who **do not respond to** ***or*** **do not tolerate a drug**.
  - **Augmentation** ***may be*** **good** ***for partial*** **responders**.

# Bipolar Disorder



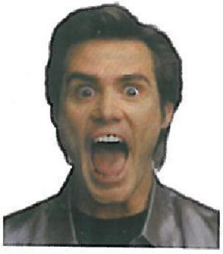
## ➢ Overview:-

- **Bipolar disorder**; *also known as* **Bipolar Affective Disorder** or **Manic Depression** or **Manic-Depressive Illness (MDI)**.
- *Definition*; it is a **mood disorder** ***characterized by*** periods of **elevated mood (mania)** & periods of **depression (hypomania)**.
  - *During* **mania**; abnormally happy, energetic or irritable.
  - *During* **hypomania**; crying, poor eye contact with others and negative outlook on life.
- *About* **3% of people** in the **United States** ***have*** **bipolar disorder** at some point in their life.

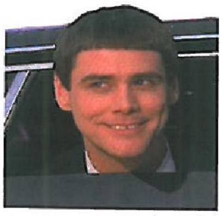
## ➢ DSM-5 Criteria for Bipolar Disorder:-

- The **DSM-5** ***defines*** **bipolar disorder** by the *experience of* **(Symptoms)**;
  1) **Manic episode** or 2) **Hypomanic episode** or 3) **Major depressive episode**.

1) **Manic Episode**;
- ***Characterized by*** **at least 1 week** of an ***abnormal*** and ***persistently*** **elevated mood** accompanied by an ***increased*** **amount of activity**.
- **Three** (***or more***) of the following symptom are present ***most of the*** **day**, ***nearly*** **every day**;
  1) Inflated self-esteem (grandiosity).
  2) Decreased need for sleep.
  3) Excessive talking or pressured speech.
  4) Flight of ideas.
  5) Poor attention (distractibility).
  6) Increased hyperactivity or agitation.
  7) Pleasurable activities without respect to the consequences.



2) **Hypomanic Episode**; is a ***milder form*** of **mania**.
- It must exist for **4 days** or **longer** of the ***same*** **criteria** as **mania**.
- ***Unlike*** **mania**, it is ***not*** **severe enough**, ***does not*** **impair social** or **occupational functioning** and is ***not*** **associated** ***with*** **psychosis**.
- **Three** (***or more***) symptom in the manic episode (***see above***) are present ***most of the*** **day**, ***nearly*** **every day**, ***but*** **less severe**.



3) **Major Depressive Episode**;
- It must exist for **2 weeks** or **longer**.
- ***Persistent*** **feeling** of **sadness** and ***loss*** of **interest** nearly every day.
- It is diagnosed when a patient ***exhibits*** at least **five** of the **DSM-5 symptoms of MDD** (see page no. 287) nearly every day for at least **2 weeks**.

## ➢ Types of Bipolar Disorder:-

1) **Bipolar I (BP I)**: **One** *or* **more** manic *or* mixed episodes (both mania and depression) ***and*** major depressive episodes.
2) **Bipolar II (BP II)**: **One** *or* **more** major depressive episodes, ***accompanied by*** at least **one** hypomanic episode.
3) **Bipolar Disorder NOS** (not otherwise specified): This is a ***catchall*** **category**, the **symptoms** may ***not*** **last long enough** or the person may have ***too few*** **symptoms** to be diagnosed with **bipolar I** or **II**.
4) **Cyclothymic Disorder** (**Cyclothymia**): **Several periods** of hypomania *and* mild depression (***no*** **mania** and **MD**) for ***at least*** **two years**.
5) **Rapid Cycling**: ***At least*** **4 episodes** of **mania** or **depression** ***in*** **1 year**.

The photos from Jim Carrey movies

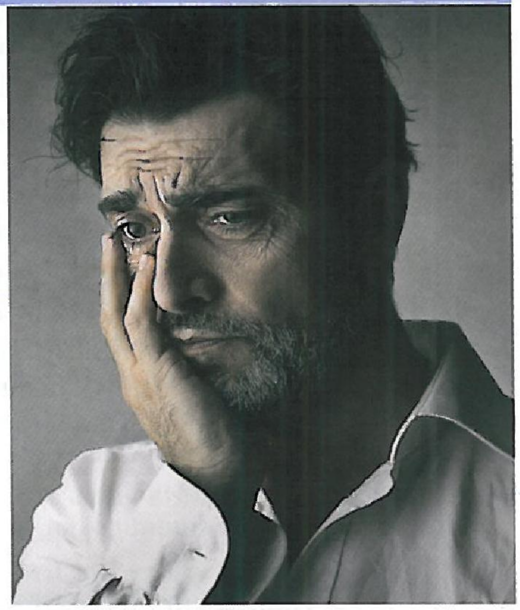
# Anxiety Disorders

medication
assault stress
development
post traumatic stress disorder
neuroendocrinology
numbing disturbance worry sufferer
distress
veterans biochemical health problems individual
symptom disorder behavioural drug addiction
falling mental irrational thinking somatic cognitive
detection
irritable threat memories criteria avoidance
pessimistic
traumatic experience mental health problems distressing dreams
emotional headaches
alternative help difficult negative
prefrontal cortex
cortex physical
thoughts anxiety worse stimulus
diagnose cope
symptoms mind individuals
testing severe feelings
escape traumatic
indicators psychological trauma alcohol abuse cause
psychological negative event
reaction abusive mood diagnostic
guilty severe illnesses avoid feel hippocampus counselling
horror outcome screening exposure accidents death
using drugs anxious increased psychological family
trigger treatments life
acute arousal
emotional numbing
violence combat intervention
control loose
drugs drink

- **Anxiety Disorders**; are **mental disorders** *characterized by feelings* of **anxiety** and **fear**.
  - **Fear**; is a **emotional response** *to* **current events.**
  - **Anxiety**; is a **worry** *about* **future events.**
- ***These*** **feelings** may cause **physical symptoms**, such as a *increase* **heart rate** and **shakiness.**
- *About* **18%** of **Americans** and **14%** of **Europeans** *may be* affected by **one** or **more anxiety disorders.**

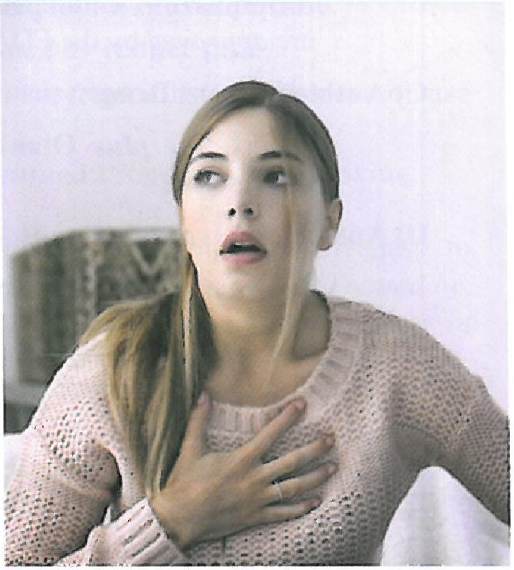
## ➢ Most Common Types of Anxiety Disorders:-

### Generalized Anxiety Disorder (GAD)



- **GAD** is a **common, chronic disorder** *characterized by* **long-lasting anxiety (6 months** or **more).**
- *Non*-**specific** (*generalized*) *persistent* **fear** and **worry**, *without* **focused** on *any* **object** or **situation.**
- *Most common* **anxiety disorder** to *affect* **older adults.**
- **DSM-5 criteria**; The **anxiety** and **worry** are *associated with* **three** (or **more**) of the following **six symptoms** with *at least* some symptoms present for **more days** for *at least* **6 months** (*Note*; *Only* **one item** is required in **children**);
  1) Restlessness or feeling keyed up or on edge.
  2) Being easily fatigued.
  3) Difficulty concentrating or mind going blank.
  4) Irritability.
  5) Muscle tension.
  6) Sleep disturbance.
- ***Prevalance***; GAD affects 6.8 million adults, or 3.1% of the U.S. population. women are twice as likely to be affected as men (*Reference; Anxiety and Depression Association of America; ADAA*).

### Panic Disorders



Patient may breathing from paper bag to overcome hyperventilation during panic attack

- **Panic disorder** is *characterized by* **separate periods** of ***sudden***, ***intense*** **fear** or **terror** & *feelings* of **impending doom.**
- ***During*** **panic attacks**, a person has ***intense*** **terror**, often marked by **tremor, dizziness** and **difficulty breathing.**
- *About* 60% of panic attacks, accompanied by **hyperventilation**
- ***Usually***, the ***precipitating*** **cause** is **unknown.**
- ***Some*** **environmental factors** can ***attributed*** in **attack.**
- **DSM-5 criteria**; ***intense*** **fear** or ***intense*** **discomfort** that ***reaches a peak*** within **minutes**, and during which time **four** (or **more**) of the ***following*** symptoms occur;

1) Palpitations.
2) Sweating.
3) Trembling (tremor) or shaking.
4) Shortness of breath.
5) Feelings of choking.
6) Chest pain or discomfort.
7) Nausea.
8) Dizziness or light-headed.
9) Chills.
10) Paresthesias (numbness).
11) Derealization (unreality).
12) Going crazy.
13) Fear of dying.

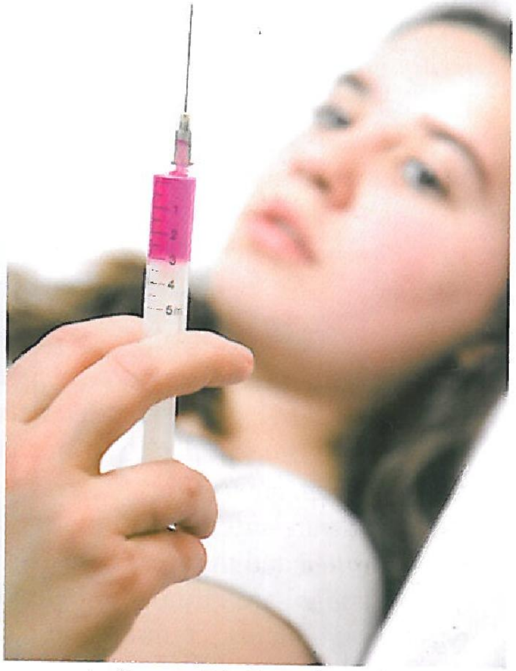
- ***Prevalance***; Panic disorder affects 6 million (2.7%), women are twice as likely to be affected as men. Very high comorbidity rate with major depression (*R;* ADAA).

## Agoraphobia

- **Agoraphobia** [ag-uh-ruh-FOE-be-uh] is a *type* of **anxiety disorder** in which **person fear** and *often avoid* **places** or **situations** that ***might cause*** **panic attack** and ***make*** **feel trapped, helpless** or **embarrassed**.
- Patient **fear** an ***actual*** or ***anticipated*** **situation**, such as **using public transportation, being in open** or **enclosed spaces, standing in line** or **being in a crowd**.
- **Agoraphobia** is ***strongly linked*** with **panic disorder** and is often ***precipitated*** by the **fear** of having a **panic attack** (in **DSM-5**, agoraphobia is ***separate*** from **panic disorders**).
- **DSM-5 criteria**; ***marked*** **fear** or **anxiety** about **two** (or **more**) of the following **five situations**;
  1) Using public transportation.
  2) Being in open spaces (parking lots, marketplaces, bridges).
  3) Being in enclosed places (shops, cinemas).
  4) Standing in line or being in a crowd.
  5) Being outside of the home alone.
- ***Prevalance***; Every year approximately 1.7% of adolescents and adults have a diagnosis of agoraphobia. Females are twice as likely as males to experience agoraphobia (R; DSM-5)

## Specific Phobias

- ***Marked*** **fear** or **anxiety** about a ***specific*** **object** or **situation** (e.g., flying, heights, animals, receiving an injection, seeing blood). Note: In children, the fear or anxiety may be expressed by crying, tantrums, freezing or clinging.
- **Phobias** can be ***classified*** under the following **general categories**:
  - **Animal type**; Fear of dogs, cats, rats and/or mice, pigs, cows, birds, spiders, or snakes.
  - **Natural environment type**; Fear of heights (acrophobia), lightning and thunderstorms (astraphobia), or aging (gerascophobia).
  - **Situational type**; Fear of failure (atychiphobia), of small confined spaces (claustrophobia), or the dark (nyctophobia).
  - **Blood/injection/injury type**; this includes fear of medical procedures, including needles and injections (trypanophobia), fear of blood (hemophobia) and fear of getting injured.
  - **Other**; Fear of contracting an illness; children's fears of loud sounds or costumed characters.



- ***Prevalance***; Specific phobias affects 19 million (8.7% ), women are twice as likely to be affected as men. The usual age of onset is childhood to adolescence (7 years). (*R;* ADAA).

- Warm or heat sensation (burning skin sensation) in the body particularly head may occur in anxiety patients.

## Social Anxiety Disorder (SAD)

- **SAD** ***also known as*** **social phobia**, is an **anxiety disorder** ***characterized by*** a ***significant amount*** of **fear** in **one** or **more social situations**.
- ***This fear*** can be ***specific*** to particular social situations (***such as*** **public speaking**) or, more typically, is experienced in **most** (or ***all***) **social interactions**.
- ***Examples include***; social interactions (having a conversation, meeting unfamiliar people), being observed (eating or drinking), and performing in front of others (giving a speech).
- ***Prevalance***; SAD affects 15 million (6.8%), Equally common among men and women, typically beginning around age 13 (*R;* ADAA).

## Post-Traumatic Stress Disorder (PTSD)

- **PTSD**; is a **mental disorder** that ***results from*** a **traumatic experience**.
- It is ***characterized by*** **exposed** to **one** or **more traumatic events**, ***such as*** **sexual assault**, **warfare**, **traffic collisions**, **terrorism** or other threats on a person's life.
- In **DSM-5**, **PTSD** is ***classified as*** a **trauma- and stress-related disorder** (***but*** it is classified as **anxiety disorder** in **DSM-4**).
- **Psychotherapy** is the **"gold standard"** of ***treatment*** for **PTSD**.
- The term of **PTSD** was coined in 1970s, due to diagnoses of US military veterans of the **Vietnam War**. It was officially recognized in 1980 in the DSM-III.
- ***Prevalance***; PTSD affects 7.7 million (3.5%), Women are more likely to be affected than men. Childhood sexual abuse is a strong predictor of lifetime likelihood for developing PTSD. (*R;* ADAA).

## Obsessive–Compulsive Disorder (OCD)

- **OCD** is a **mental disorder** where **people** **feel** the ***need to*** **check things** ***repeatedly***, **perform certain routines** ***repeatedly*** or have certain **thoughts** ***repeatedly***.
- **Obsessive**; are **intrusive thoughts** that ***cannot*** be ***controlled*** and that are ***repetitive***.
- **Compulsions**; are **ritualistic behaviours** (e.g., washing the hands, combing the hair, cleaning the house).
- **OCD** is ***not classified*** as an **anxiety disorder** by the **DSM-5**.
- **OCD** is ***associated with*** **anxiety disorder** and an ***increased*** **risk of suicide**.
- Treatment for OCD includes behavioural therapy and sometimes selective SSRIs.
- ***Prevalance***; OCD affects 2.2 million (1.0%). Equally common among men and women. The median age of onset is 19, with 25 percent of cases occurring by age 14. One-third of affected adults first experienced symptoms in childhood (*R;* ADAA).

### ➢ Causes:-

- The *exact cause* of **anxiety disorders** is **unknown**; but anxiety disorders, like other forms of mental illness, are not the result of personal weakness, a character flaw or poor upbringing.
- Anxiety disorders ***may be*** caused by **environmental factors**, **medical factors**, **genetics**, **brain chemistry** or **substance abuse**. It is *most commonly **triggered by*** the **stress in our lives**.

### ➢ Pathophysiology:-

- The ***exact*** **mechanism** remains **unclear**.
- ***Multiple*** **neurotransmitters** involving wide areas of the brain have been ***implicated*** in **anxiety**, including receptors for **benzodiazepines**, **N-methyl-D-aspartate/glutamate** and **serotonin**.
- Specific parts in the brain ***such as*** **amygdala** (limbic system) which are *responsible for **processing*** of **fear and anxiety**, and its **function** may be ***disrupted*** in **anxiety disorders**.

### ➢ Treatments:-

- **Treatment options** are **different**, ***depending on*** **type of anxiety disorder**.
- Treatment options available ***include***; **psychotherapy** (*such as* cognitive behavioural therapy; CBT), **life style modification** (such as stopping smoking) and **medications** (such as benzodiazepines).

# Pharmacological Options

## Benzodiazepines (BDZs)

- **BDZs** have **anxiolytic properties** and some have preventive ***efficacy*** for **panic attacks**.
- Depending on the ***choice of agent*** according to **onset** and **duration of action**;
  - ***Short*** **half-life/*high* potency**;
    - These are usually ***more*** **rapid-acting** agents that provide ***quicker*** **control of the symptoms**.
    - **Tolerance** of the **hypnotic effect** ***develops rapidly***, **dependence** and **withdrawal problems** ***are common***.
    - These are often used for ***acute*** **management**.
  - ***Long*** **half-life/low potency**;
    - These are usually ***produce*** **longer-lasting effects** throughout the day.
    - **Withdrawal symptoms** may be ***less*** **pronounced**.
- The ***primary*** **side effects** ***associated*** with **benzodiazepines** are;
  - **Tolerance**; Tolerance of the hypnotic actions occurs within days.
  - **Dependence**; Dependence occurs within weeks to months of continued use.
  - **Withdrawal symptoms**; May occur in abrupt cessation.
- Full text about BDZs (see page no. 277).

## Antidepressants

1) **Selective Serotonin Reuptake Inhibitors (SSRIs)** are ***also effective*** for **several anxiety disorders**. They are the ***agents of choice*** for **long term treatment of anxiety disorders**.
2) **Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs)**; **Venlafaxine** has been ***approved for*** the ***treatment*** of **generalized anxiety** and **social anxiety disorders**. **Duloxetine** is also ***approved for*** **generalized anxiety**.
3) **Buspirone**; has **anxiolytic properties**, may be ***used for* GAD**, it has *little **efficacy*** for **other anxiety disorders**, due to it has **long onset of action** (weeks), ***short-term*** **benzodiazepines** may used as a **bridge** until Buspirone takes effect.
4) **Tricyclic antidepressants** have ***preventive efficacy*** for **panic disorder** and **anxiolytic activity**.

- **N.B.**;
  - ***About*** **25%** of these patients experience a **hyper-stimulatory response** to antidepressants, which can be confused with a worsening of the anxiety symptoms. This response is ***more common*** when **therapy is first begun**. ***Using*** **low doses** at **first** ***can help***.
  - **Antidepressants** can also be ***helpful*** for **anxiety** that ***accompanies*** **depression**.
- Full text about antidepressants (see page no. 291).

# Miscellaneous Agents

1) **β-Blockers**; ***used to* block** the **peripheral symptoms** of **panic disorder**.
2) **Antihistamines *with* sedating properties** (**Hydroxyzine**); ***reduce* physical symptoms of anxiety**.
3) **Antipsychotics** are ***not considered* first-line agents** for the treatment of anxiety disorders. Selected **second generation antipsychotics** (**SGAs**) used as ***add-on therapy*** for **OCD**, **GAD**, and **PTSD**.
4) **MAOIs** can be ***effective*** for the ***treatment*** of **panic disorder** *when the patient* also has **atypical depression** (seldom used because of the potential for serious adverse effects).
5) **Barbiturates** are ***seldom used*** (less effective and can be lethal if taken in overdose).

## ➢ Recommended Therapy for Specific Anxiety Disorders:-

### Generalized Anxiety Disorder (GAD)

A) **Antidepressants**; These are considered ***first-line agents***, ***these include***;
- **SSRIs**; **Escitalopram**, **Paroxetine** and **Sertraline**.
- **SNRIs**; **Venlafaxine** and **Duloxetine**.
- **TCAs**; **Imipramine**.

B) **Benzodiazepines**; This class of drugs is ***rapidly effective***, **long-term therapy** is ***common but*** **not recommended**.
- BDZs can be taken in ***combination*** with either **antidepressants** or **Buspirone** as a bridge until these drugs start to take effect.
- They are **more effective *against* somatic symptoms**.

C) **Buspirone**; ***Good*** when BDZs ***should be*** **avoided** (e.g., in patients with a history of substance abuse); takes 2-4 weeks to be effective.

D) **Pregabalin**; *Considered* a ***second-line agent*** behind antidepressants.

E) **Cognitive Behavioural Therapy** (**CBT**) and **other psychotherapies** ***should generally*** be ***included*** with **pharmacotherapy**.

F) **Augmentation therapy**; with **Quetiapine**, **Olanzapine** or **Risperidone** can be ***tried*** in **treatment-refractory patients**.

### Panic Disorders

A) **Antidepressants**; These are considered ***first-line agents***, ***these include***;
- **SSRIs**; **Escitalopram**, **Fluoxetine**, **Fluvoxamine**, **Paroxetine** and **Sertraline**.
- **SNRIs**; **Venlafaxine** and **Duloxetine**.
- **N.B.**; ***Patients with*** **panic disorder** tend to have a ***higher*** **sensitivity** to **physical symptoms**. So, these patients should be initiated on **low doses** of antidepressants (25 mg of sertraline or 5 mg of paroxetine).

B) **Benzodiazepines**; **High-potency rapid onset agents**; ***effective***.

C) **CBT** and **other psychotherapies** are ***effective***.

- **N.B.**; **Buspirone**, **Bupropion**, **β-blockers**, **antihistamines** and **antipsychotics**; are not effective.

### Specific Phobias

- ***Not treated*** with **medications**.
- **Systematic desensitization** (**graduated exposure therapy**) and ***other*** **behavioural therapy** often effective.

### Social Anxiety Disorder (SAD)

A) **CBT** is the most important modality.

B) **Antidepressants**: ***First-line medication*** for treatment;
- **SSRIs**; **Escitalopram**, **Fluvoxamine**, **Paroxetine** and **Sertraline**.
- **SNRIs**; **Venlafaxine**.
- ***Response*** to antidepressants tends to be **slow** (***up to*** **12 weeks**).

C) **Clonazepam** may be used as an adjunct.

D) **Gabapentin** and **Pregabalin** may be used.

## Post-Traumatic Stress Disorder (PTSD)

A) **SSRIs** (**Fluoxetine**, **Sertraline** and **Paroxetine**) are considered *first-line agents*.

B) **Augmentation therapy**; with other agents to ***treat*** **specific symptoms** (**β-blockers** or **mood stabilizers**).

C) **Prazosin** is used to ***treat*** **PTSD-associated nightmares**.

D) **Anticonvulsants** (**Valproic acid**, **Carbamazepine**, **Lamotrigine** and **Topiramate**) for **aggression**, **anger** and **depression**.

E) *Atypical* **antipsychotics** (**Olanzapine**, **Quetiapine** and **Risperidone**) for **psychotic symptoms**.

F) **CBT** and **other psychotherapies** are *effective*.

- **N.B.**; **BDZs** are ***not*** *effective*.

## Obsessive–Compulsive Disorder (OCD)

A) **Antidepressants**; These are considered *first-line agents*, ***these include***;

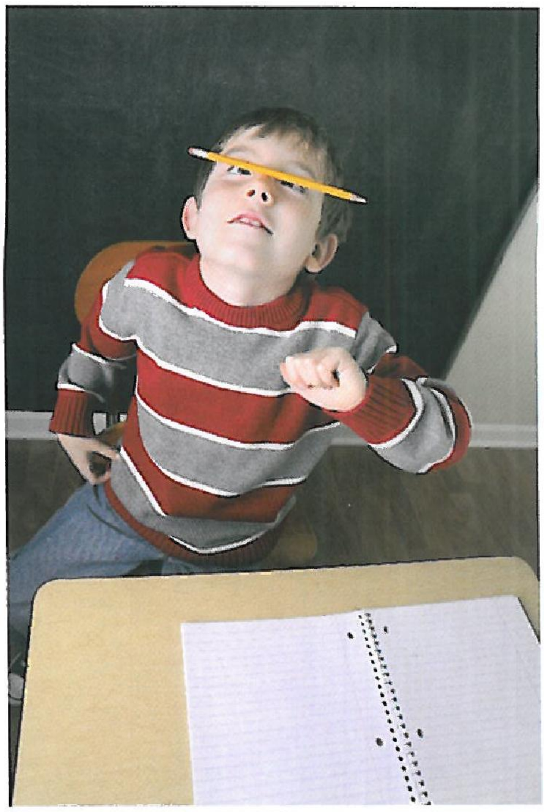
- **SSRIs**; **Escitalopram**, **Fluoxetine**, **Fluvoxamine**, **Paroxetine** and **Sertraline**.
- **TCAs**; **Clomipramine**.

B) **CBT** ***may be effective***, but it is ***secondary*** to **pharmacotherapy**.

C) **Augmentation therapy** (**SSRIs** ***alone***, often fail to control OCD completely); ***with*** **Haloperidol** or **second generation antipsychotics (SGAs)** (**Olanzapine**, **Quetiapine** and **Risperidone**) may help, ***in general***, **high doses** ***need*** to be **used**.

# Attention Deficit Hyperactivity Disorder (ADHD)

## ➢ Overview:-

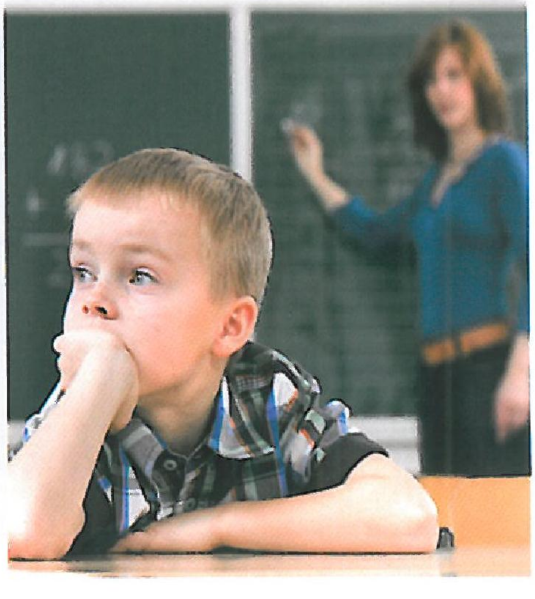


- **Attention Deficit Hyperactivity Disorder (ADHD)**; is a ***neurodevelopmental*** (impair of the development of the brain) **psychiatric disorder**.
- **ADHD** is a **disorder** that ***manifests*** in **childhood** with ***symptoms*** of **hyperactivity**, **impulsivity** and/or **inattention**.
- **The symptoms *affect* cognitive**, **academic**, **behavioral**, **emotional** and **social functioning**.
- *Prevalence*;
  - The **World Health Organization (WHO)** *estimates* that it affected about **39 million** people as of **2013**.
  - **Studies** ***suggest*** that the **worldwide prevalence** of **ADHD** in ***children*** is between **2-12%**.
  - ***In children***, **ADHD** is **3-5 times *more common*** in **boys *than*** in **girls**.
  - The prevalence rate of **ADHD *in the adult*** general population is **4-5%**.
  - ***In adults***, the **sex ratio *nearly*** **equal**.
  - **DSM-5 prevalence**; about 5% of children and about 2.5% of adults.
- ***ADHD in children*** the **symptoms *begin*** by age **6-12** and ***persist*** for ***more than*** **6 months**.
- ***Before*** **1987** the condition was ***known as*** **Attention Deficit Disorder** (**ADD**).

## ➢ DSM-5 Criteria: *According to* DSM-5; the 3 types of ADHD;

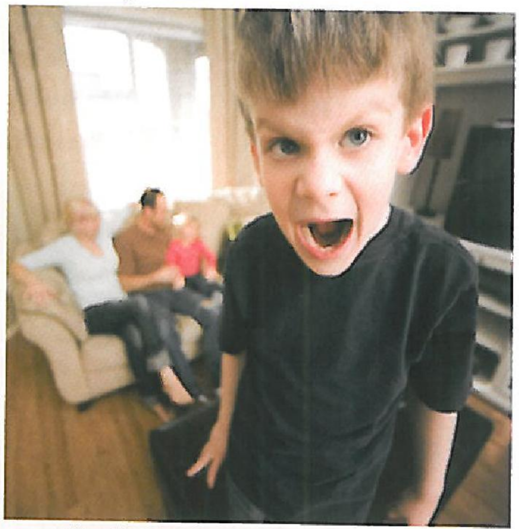
1) ***Predominantly*** **inattentive**.
2) ***Predominantly*** **hyperactive/impulsive**.
3) ***Combined*** **hyperactive-impulsive** and **inattentive**.

- **Inattentive**; **Six** (or **more**) of the following symptoms have persisted for ***at least*** **6 months** to a degree that is maladaptive and inconsistent with developmental level;
  - **N.B.**; in age 17 and older, ***at least*** **five symptoms** are ***required***.



1) Often fails to attention to details or makes careless mistakes in schoolwork, work or other activities.
2) Often has *difficulty* to sustaining attention in tasks or play activities.
3) Often does not listen to what is being said.
4) Often does not follow instructions and fails to finish schoolwork, chores, or duties in the workplace (not *due to* understand instructions).
5) Often has *difficulty* to organize tasks and activities.
6) Often avoids or strongly dislikes tasks (such as schoolwork or homework) that require sustained mental effort.
7) Often loses things necessary for tasks or activities (school assignments, pencils, books, tools or toys).
8) Often is easily distracted by extraneous stimuli.
9) Often forgetful in daily activities.

- **Hyperactivity/impulsivity**; **Six** (or **more**) of the following symptoms have persisted for ***at least*** **6 months** to a degree that is maladaptive and inconsistent with developmental level;
  - **N.B.**; in age 17 and older, ***at least*** **five symptoms** are ***required***.



1) Fidgeting with or tapping hands or feet, squirming in seat (not stable in setting).
2) Leaving seat in other situations in which remaining seated is expected such as in classroom.
3) Running about or climbing excessively in situations where this behaviour is inappropriate (in adolescents or adults, this may be limited to subjective feelings of restlessness).
4) Difficulty playing in leisure activities quietly.
5) Unable to be or uncomfortable being still for extended periods of time.
6) Excessive talking.
7) Blurting out answers to questions before the questions have been completed.
8) Difficulty waiting in lines or awaiting turn in games or group situations.
9) Interrupting or intruding on others (for adolescents and adults, may intrude into or take over what others are doing).

- *Notes*;
  - **Onset** is ***no later than*** **age 12 years**.
  - **Symptoms** ***must be*** **present** in **2** or **more situations**, ***such as*** school, work or home.
  - The **disturbance** ***causes*** clinically ***significant distress*** or ***impairment*** in **social**, **academic** or **occupational functioning**.
  - **Disorder** ***does not*** **occur** exclusively ***during*** the course of **schizophrenia** or other **psychotic disorder** and is ***not better accounted*** for by **mood**, **anxiety**, **dissociative**, **personality disorder** or **substance intoxication** or **withdrawal**.

## ➢ Causes and Pathophysiology:-

- The ***exact*** **pathology** of **ADHD** is ***not clear***.
- Both **genetic** and **environmental factors** ***contribute to*** **ADHD**.

- **Neurotransmitters dopamine** and **norepinephrine** are ***implicated*** in the pathophysiology of ADHD;
  - * **Dopamine** (**DA**); ***Involved*** in reward, risk taking, impulsivity and mood.
  - * **Norepinephrine** (**NE**); ***Modulates*** attention, arousal and mood.
    - ***Brain studies*** on individuals with ADHD suggest a ***defect*** in the **DA receptor $D_4$ receptor gene** (responsible for modulate attention to and responses to one's environment) and ***overexpression*** of **dopamine transporter-1** (**$DAT_1$**; transport DA/NE into the presynapse ⇨ ↓ DA/NE in synapse).
- **Family environment factors**; ***such as*** high degree of psychosocial stress, maternal mental disorder, paternal criminality, low socioeconomic status, foster care have been linked to increased rates of ADHD.
- **Brain imaging studies**; show ***reduction*** of **volume** in ***certain*** **brain structures** such as left-sided prefrontal cortex and posterior parietal cortex (***neurodevelopmental disorder***).

## ➢ Complications:-

- ADHD can make life difficult for children.
- **Children** *with* **ADHD** are **more likely** ***than*** are **other children** to also have conditions such as: **learning disabilities**, **anxiety disorders**, **depression**, **bipolar disorder**, **oppositional defiant disorder**; **ODD** (negative, defiant and hostile behaviour toward authority figures), **obsessive compulsive disorder**; **OCD**, **conduct disorder** (antisocial behaviour such as stealing, fighting, destroying property, and harming people or animals) and **Tourette syndrome** (neurological disorder characterized by repetitive muscle or vocal tics).

➢ **Managements:-**

- **Psychotherapy** has **pharmacotherapy**;
  - *In some cases*; **psychotherapy** ***alone*** has been **effective**.
  - *In some cases*; **psychotherapy** is **successful** when used with **pharmacotherapy**.
- **Dietary modifications**; may also be of ***benefit***; ***supporting*** **free fatty acids** and ***reduced*** **exposure to food colouring**.
- **Regular physical exercise**; **aerobic exercise** is an *effective* **add on** treatment for ADH.

## Psychotherapy

- ***Psychological therapies*** used ***include***: psycho-educational input, behaviour therapy, cognitive behavioural therapy (CBT), interpersonal psychotherapy, family therapy, school-based interventions, social skills training, behavioural peer intervention, organization training, parent management training and neurofeedback.

➢ **Examples:-**

- **Behaviour therapy**; teachers and parents can learn behaviour-changing strategies for dealing with difficult situations.
- **Psychotherapy**; this allows older children with ADHD to talk about issues that bother them, explore negative behavioural patterns and learn ways to deal with their symptoms.
- **Parenting skills training**; this can help parents develop ways to understand and guide their child's behaviour.
- **Family therapy**; Family therapy can help parents and siblings deal with the stress of living with someone who has ADHD.
- **Social skills training**; this can help children learn appropriate social behaviours.

## Pharmacotherapy

### Stimulants (Psychostimulants)

- **Stimulants** are the ***first-line therapy*** and probably the ***most effective*** **treatment**.
- **Stimulants** are ***preferred*** to **other medications** ***because*** stimulants have a **rapid onset of action** and **long record of safety** and **efficacy**.
- **All stimulants** have ***similar efficacy but differ*** by **dosing**, **duration of action**, and **adverse effect** profiles in individual patients.
- **Stimulant therapy** ***should be*** made to ***start*** at the ***lowest*** **dose** and ***titrate up*** for **clinical efficacy**.
- ***Some*** **stimulants** come in **sustained-release** preparations, which may ***decrease*** the number of **total daily doses**.
- ***Stimulants*** may cause ***significant*** **insomnia** ***if taken*** at **night**.
- ***Most common*** **adverse effects** of stimulants include **appetite suppression** and **weight loss**, **headaches** and **mood effects** (depression, irritability).
- There has been a ***long concern*** that the use of **stimulate therapy** ***leads*** to **substance abuse**. ***Recent studies*** have demonstrated that **stimulant therapy** ***does not*** **increase** the **risk of future substance use** ***or*** **abuse**.
- **Stimulant medications** do ***enhance*** **mental executive** ***functions*** for those with **ADHD**.
- ***Most commonly*** prescribed **stimulants** ***for*** **ADHD** are **phenethylamines**: **Amphetamine** (Adderall®), **Methylphenidate** (Ritalin®), **Dexmethylphenidate** (Focalin®), **Dextroamphetamine** (Dexedrine®), **Dextromethamphetamine** (Desoxyn®) & **Lisdexamfetamine** (Vyvanse®).
- ***See*** **ANS chapter**, for more details about **Amphetamine** and **Amphetamine derivatives**; 68.

## Non-Stimulants

### Atomoxetine (Strattera®)

- **Atomoxetine** [A-toe-MOX-e-teen] is a **norepinephrine reuptake inhibitor** approved for the ***treatment*** of **attention deficit hyperactivity disorder** (**ADHD**).
- It has become a ***second-line*** and, in ***some cases***, ***first-line*** treatment in **children** and **adults *with* ADHD *because*** of its **efficacy**.
- The ***initial*** **therapeutic effects** usually take **2-4 weeks** to ***become*** **apparent**.
- It can be ***abruptly*** **stopped *without significant*** **withdrawal effects**.
- ***Dose***; ranges from 40mg/day to 100mg/day given in 1-2 divided doses
- ***Side effects***; Insomnia, dry mouth, cough, decreased appetite, upset stomach, nausea or vomiting, dizziness, drowsiness, problems urinating, irritability, constipation, skin rash, itching, increased menstrual cramps, increase blood pressure and sexual side effects including impotence, loss libido or trouble having an orgasm.
- ***Drug interactions***; **CYP2D6 inhibitors *such as*** **Bupropion** or **Fluoxetine** ⇨ ↑ plasma atomoxetine levels (**Atomoxetine** is a substrate for **CYP2D6**) and **MAOIs**.
- **Reboxetine** is ***another*** **norepinephrine reuptake inhibitor**, it has also been ***used off-label*** for **ADHD** (see page no. 297).

### Clonidine (Kapvay®)

- **Clonidine** is a ***centrally acting*** **$\alpha_2$-adrenergic agonist** used as **antihypertensive agent**.
- In **2010 US FDA** has ***approved*** Kapvay® (**Clonidine Hydrochloride**) ***extended-release*** for the ***treatment*** of **ADHD** as ***monotherapy*** and as ***adjunctive therapy*** to **stimulant medications**, for paediatric patients aged 6-17 years. It was later approved for adults.
- ***Dose***; should be ***initiated with*** **one 0.1 mg** tablet at **bedtime**, ***if*** **dose *equal*** or ***higher than*** **0.2 mg/day**, **doses** should be taken **twice** a day (max. dose; 0.4mg/day).
- ***Most common side effects*** and ***precautions***;
  - **Hypotension** and **bradycardia**; dose-related decreases in blood pressure and heart rate.
  - **Sedation** and **somnolence**.
  - **Rebound hypertension**; in ***abrupt discontinuation***.
- **Warning**; ***Sudden*** **deaths** have been ***reported*** in **children** taking **Clonidine** with **Methylphenidate** at **bedtime**.

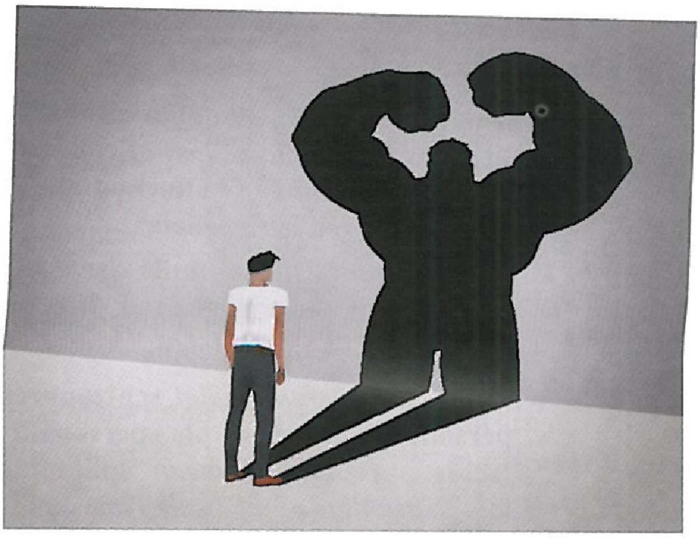
### Guanfacine (Intuniv®)

- **Guanfacine *like* Clonidine**, is a ***centrally acting*** **$\alpha_2$-adrenergic agonist**, used in the ***treatment*** of **ADHD** and **hypertension**.
- Like **Clonidine**, in **2010 US FDA** has ***approved*** Intuniv® (**Guanfacine Hydrochloride**) ***extended-release*** for the ***treatment*** of **ADHD** as ***monotherapy*** and as ***adjunctive therapy*** to **stimulant medications**, for paediatric patients aged **6-17 years**.
- ***Dose***; should be ***initiated with*** 1 mg/day once and adjust in increments of no more than 1 mg/week. Target dose range (0.05 - 0.12 mg/kg/day). ***Dosage adjustments*** are recommended with concomitant use of ***strong*** **CYP3A4 inhibitors**.
- ***Most common side effects*** and ***precautions***; same as **Clonidine**.

## Antidepressants

- **Bupropion**, **Venlafaxine Escitalopram** and **Sertraline** have been found effective.
- **TCAs** (**Imipramine - Desipramine - Nortriptyline**) have been found effective, ***because*** of potential adverse effects, they are rarely used.

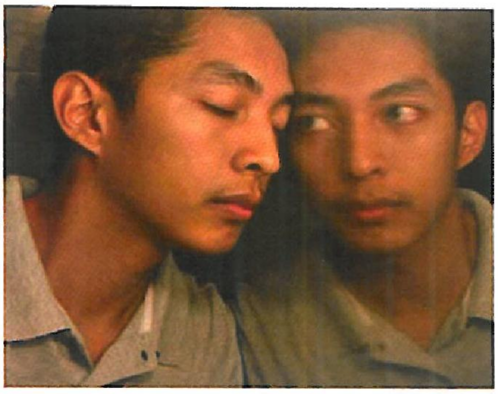
- **Delusions *;**



  - **Delusions** are ***strongly held* false beliefs** that are ***not consistent*** with the **reality**.
  - Delusions **persist *even*** when there is **evidence** that the beliefs are not true or logical.
  - ***Some people*** develop a **delusional idea** to ***explain*** a **hallucination** *they are having.* ***For example***, if they have heard voices describing their actions, they may have a delusion that someone is monitoring their actions.
  - A **fixed delusion** will ***not change***, ***no matter*** *how much* **evidence** is ***offered*** to the **contrary**.
  - They may have **paranoid *delusions*** and ***believe*** that **others** are ***trying*** to **harm them**, such as by cheating, harassing, poisoning, spying on or plotting against them or the people they care about. These beliefs are called "**persecutory delusions**".
  - They ***may believe*** **people** on **TV** or in **newspaper articles** are ***communicating*** **messages** to them **alone**, or that there are ***hidden*** **messages** in the **colours** of **cars** passing on the street.
  - **Religious delusions**; that he thought, he is a Jesus, God, a prophet, or the antichrist.
  - **Delusions *occur in*** as many as **4** out of **5** people with **schizophrenia**.
- **Thought Disorders *;**
  - **Thought disorders** are ***unusual*** or ***dysfunctional*** ways of **thinking**.
  - ***One form*** is called "**disorganized thinking**" This is when a person has ***trouble*** **organizing** his or her **thoughts**, **disorganized thinking** is ***inferred from*** **disorganized speech**.
  - This is often called "**word salad**" (confused or unintelligible mixture of seemingly random words).
- **Movement Disorders;**
  - **Abnormal motor behaviour** can include ***resistance*** to **instructions**, *inappropriate* and *bizarre* **posture**, a ***complete lack*** of **response**, or ***useless*** and **excessive movement**.
  - A person may become **catatonic** (***Catatonia*** is a state in which a **person *does not*** **move** and ***does not*** **respond *to*** **others**).

➢ **Negative Symptoms** (Often limited respond to medications)**:-**

- **Flat affect (diminished emotional expression);**
  - Lack emotion, ***such as*** not making eye contact, not changing facial expressions, speaking without inflection or monotone or not adding hand or head movements that normally provide the emotional emphasis in speech.
- **Reduced ability to plan or carry out activities, *such as*;**



  - ***Decreased*** **talking**.
  - ***Lack*** of **personal hygiene**.
  - ***Loss*** of **interest in everyday activities**.
  - **Social *withdrawal***.
  - ***Lack*** of **ability** to **experience pleasure**.

➢ **Cognitive Symptoms** (Not respond to medications)**:-**

- **Poor "executive functioning";**
  - The ability to understand information.
- **Trouble focusing or paying attention.**
- **Problems with "working memory";**
  - The ability to use information immediately after learning it.

## ➢ DSM-5 Criteria (Main characteristics):-

- **Two** (or **more**) ***of the following***, each present for a significant portion of time during a **one month** period (or less if successfully treated);
    1) Delusions*.
    2) Hallucinations*.
    3) Disorganized speech* (e.g., frequent derailment or incoherence).
    4) Grossly disorganized or catatonic behaviour.
    5) Negative symptoms (i.e., diminished emotional expression or avolition).
- *At least* 1 of the **symptoms** ***must be*** the **presence** of 1) **delusions**, 2) **hallucinations**, or 3) **disorganized speech**.

## ➢ Schizophrenia Subtypes:-

- **In DSM-5**, The American Psychiatric Association (APA) ***removed*** the **five subtypes** of schizophrenia, ***because*** they did not appear to be helpful for providing better-targeted treatment for predicting treatment response (but are defined in the DSM-4).

### Paranoid Schizophrenia

- It is the ***most common type*** of schizophrenia.
- **Delusions** or **auditory hallucinations** are *present*.
- **Thought disorder**, **disorganized behaviour**, or **affective flattening** ***are not***.
- **Delusions** are **persecutory** and/or **grandiose**, but in addition to these, other themes such as **jealousy**, **religiosity**, or **somatization** ***may also be*** **present**.

### Disorganized Schizophrenia

- It also known as **hebephrenia** (Greek term).
- **Hallucinations** and **delusions** are ***less pronounced***, although there may be some evidence of these symptoms.
- **Thought disorder** and **flat affect** are ***present together***.
- Often, there is ***impairment*** in the **emotional processes** of the individual. ***For example***, these people may appear emotionally unstable, or their emotions may not seem appropriate to the context of the situation.
- ***Inappropriate*** **facial responses** may be common.

### Catatonic Schizophrenia

- **Catatonia** is a state of ***immobility*** and ***unresponsiveness***.
- ***Disturbances*** in **movement**; may be almost **immobile** or **exhibit agitated**.
- Symptoms can include **catatonic stupor** and **waxy flexibility**.
- This set of ***symptoms*** sometimes is ***confused*** with **another disorder** called **tardive dyskinesia** (see later).
- **BDZs** are a ***first-line*** treatment strategy.
- **Antipsychotics** should be used with ***cation*** as they can ***worsen*** **catatonia**.

# Antipsychotic Drugs

- The **antipsychotic drugs** (*also called* **neuroleptics** or **major tranquilizers**) are **used** *primarily* to treat **schizophrenia**, but they are *also effective* in **other psychotic** and **manic states**.

- The word **neuroleptic** originates from the Greek word neuron ("nerve") and lepsis ("taking hold").
- The *use* of **antipsychotic drugs** involves a **difficult** ***trade-off*** ***between*** the **benefits** to ***decrease*** **psychotic symptoms** and the ***risk*** of a ***wide variety*** **side effects**.
- **Antipsychotic drugs** are ***not*** **curative** and ***do not eliminate*** **chronic thought disorders**, but they often *decrease* the **intensity** of **hallucinations** and **delusions**.
- The **antipsychotic drugs** are ***divided into*** **first generation** and **second generation** agents.
- **First-generation antipsychotics**, ***known as*** **typical antipsychotics**, while **second-generation antipsychotics**, ***known as*** **atypical antipsychotics**.
- The **first-generation** drugs are ***further classified as*** "**low potency**" or "**high potency**".
- ***This*** **classification** ***does not indicate*** **clinical effectiveness** of the drugs, ***but*** rather specifies ***affinity*** for the **dopamine $D_2$ receptor**, which, in turn, may ***influence*** the **adverse effect** of the drug.

## First-Generation Antipsychotics; FGAs (Typical)

- The **first-generation antipsychotic drugs** (***also called*** **conventional**, **typical** or **traditional antipsychotics**) are ***competitive inhibitors*** at a **variety** of **receptors**, ***but*** their **antipsychotic effects** due to ***competitive blocking*** of **dopamine $D_2$ receptors**.

### Low Potency

- ***Fewer*** **extrapyramidal symptoms; EPS**, ***but more*** **$H_1$**, **$\alpha_1$** and **muscarinic** ***blocking effects***.

| Phenothiazines | |
|---|---|
| **Chlorpromazine (CPZ)** (Neurazine®) | **Thioridazine** (Mellaril®) |

### High Potency

- ***More*** **extrapyramidal symptoms (EPS)**, ***but less*** **$H_1$**, **$\alpha_1$** and **muscarinic** ***blocking effects***.

| Phenothiazines | | |
|---|---|---|
| **Fluphenazine** (Modecate®) | **Perphenazine** (Trilafon®) | **Trifluoperazine** (Stelazine®) |
| **Mesoridazine** (Serentil®) | **Prochlorperazine** (Compazine®) | **Promethazine** (Phenergan®) |

| Butyrophenones | |
|---|---|
| **Haloperidol** (Haldol®) | **Droperidol** (Inapsine®) |

| Others | | |
|---|---|---|
| **Loxapine** (loxitane®) | **Zuclopenthixol** (Clopixol®) | **Flupenthixol** (Fluanxol®) |
| **Pimozide** (Orap®) | **Thiothixene** (Navane®) | |

- The ***discovery*** of **antipsychotics** ***between*** the **1950s** and **1970s**.
- **Chlorpromazine** [klor-PROE-ma-zeen] is the ***first*** **antipsychotic drug** found to be ***useful*** to ***reduce*** **psychotic symptoms** in **schizophrenia**.
- **Thioridazine** [THYE-oh-RID-azeen] is a ***low potency*** **typical antipsychotic** belonging to the **phenothiazine** group.
- **Fluphenazine** [floo-FEN-a-zeen], **Perphenazine** [per-FEN-a-zeen], **Trifluoperazine** [TRYE-floo-oh-PER-a-zeen], **Mesoridazine** [mez-oh-RID-a-zeen] and **Prochlorperazine** [pro-klor-PER-a-zeen] are ***high potency*** **typical antipsychotics** belonging to the **phenothiazine** group.
- **Haloperidol** [HAL-oh-PER-i-dol], a **butyrophenone**, is the ***most widely used*** **typical antipsychotic**.
- **Loxapine** [LOX-a-peen], **Zuclopenthixol** [zoo-kloe-pen-thix-ole], **Flupenthixol** [floo-pen-tiks-ol], **Pimozide** [PIM-oh-zide] and **Thiothixene** [THYE-oh-THIX-een] are ***high potency*** **typical antipsychotics** belonging to the **miscellaneous structures**.

# Second-Generation Antipsychotics; SGAs (Atypical)

- The **second-generation antipsychotic drugs** (*also called* atypical **antipsychotics**) have a *lower incidence of* EPS and have *little* or *no* have effect on **$H_1$**, **$\alpha_1$** and **muscarinic** receptor than the first-generation agents, they are *associated with* a **higher risk** of **metabolic side effects**, such as **diabetes, hypercholesterolemia** and **weight gain.**
- **Second-generation agents** are *generally* used as *first-line therapy* for **schizophrenia** to *minimize* the *risk of* EPS *associated* with the **first-generation agents.**
- The **second-generation drugs** appear to owe their unique activity to *blockade* of *both* **serotonin** and **dopamine** and **other receptors.**

| | | |
|---|---|---|
| **Clozapine** (Clozaril®) | **Aripiprazole** (Abilify®) | **Olanzapine** (Zyprexa®) |
| **Paliperidone** (Invega®) | **Quetiapine** (Seroquel®) | **Risperidone** (Risperdal®) |
| **Lurasidone** (Latuda®) | **Iloperidone** (Fanapt®) | **Ziprasidone** (Zeldox®) |
| **Asenapine** (Saphris®) | **Sertindole** (Serdolect®) | **Sulpiride** (Dogmatil®) |

- **Clozapine** [KLOE-za-peen] is the prototype, after the discovery of clozapine in 1959 led to the realization that antipsychotic drugs *not cause* **EPS.**
- **Aripiprazole** [a-rih-PIP-razole] is the *most widely prescribed* **antipsychotic agent** (from April 2013 to March 2014, sales of Abilify® amounted to almost $6.9 billion).
- **Olanzapine** [oh-LANZ-ah-peen], **Paliperidone** [pal-ee-PEAR-i-dohn], **Quetiapine** [qwe-TY-uh-peen], **Risperidone** [ris-PEAR-ih-dohn], **Lurasidone** [loo-RAS-i-done], **Iloperidone** [eye-low-PEAR-ee-dohn], **Ziprasidone** [zi-PRAS-i-done], **Asenapine** [a-SEN-a-peen], **Sertindole** [ser-TE-een-dol], **Sulpiride** [sol-PEAR-id] are **atypical antipsychotics.**

**Pharmaco Kinetics**

- *Most* **antipsychotic drugs** are *readily* **absorbed** *but* **incompletely.**
- *Only* **Ziprasidone** and **Paliperidone**; *increased* **absorption** *with* **food.**
- *Most* **antipsychotic drugs** are *highly* **lipid soluble** and **protein bound** (92-99%), and have a *large* **volume of distribution.**
- *Administration and Formulations*;
  - **Oral therapy** is *most common*.
  - **Haloperidol** can be *given* **IM** (**IV** has been linked to toxicity and *should not be given*).
  - *Long acting parenteral* (IM) (*only for* **chronic therapy** in patients who have *trouble* **adhering** to **oral therapy**);
    - **Depot forms** (*long-acting forms*) of **Haloperidol**, **Fluphenazine**, **Zuclopenthixol** and **Risperidone** are *available*, providing *sustained* **concentrations** for about **1 month** *for* **Haloperidol** and **2-3 weeks** for **Fluphenazine**, **Zuclopenthixol** and **Risperidone** (*only for chronic therapy*).
    - **Paliperidone Palmitate** (*FDA approved 5/2015*); It is a **3-month** *extended-release* **injectable suspension.**
    - **Olanzapine Palmitate**; *once monthly*, it is also available.
    - **Aripiprazole Monohydrate** (Abilify® Maintena); *once monthly*, it is also available.
  - **Asenapine** is *available* in a **sublingual formulation.**
- *Metabolism*;
  - They are **metabolized** to *many* **different metabolites**, usually by the **cytochrome P450** system, particularly the **CYP2D6, CYP1A2 & CYP3A4** (**drug interactions** *should be considered*).
  - **Paliperidone** is the *primary* **active metabolite** of **Risperidone.**

## Mechanism OF Action

1) **Dopamine Antagonists**;

- ***All*** of the **first-generation** and ***most*** of the ***second-generation*** **antipsychotic drugs** ***block*** **$D_2$ dopamine receptors** in the **brain** and the **periphery**.

2) **Serotonin Antagonists**;

- ***Most*** of the **second-generation agents** appear to exert part of their ***unique action*** through ***inhibition*** of **5-HT receptors**, ***particularly*** **5-$HT_{2A}$** receptors.

- ***Differences in Second-Generation*** (*Most Common Agents*);
  - **Clozapine**; ***Strong*** **5-$HT_{2A}$ antagonist**, ***weak*** **$D_2$ antagonist** (***Antipsychotic mechanism***), it also acts as an ***antagonist*** at **α**, **M**, **$H_1$** and other **D** & **5-HT** receptors.
  - **Aripiprazole**; **$D_2$** & **5-$HT_{1A}$** ***partial agonist*** and **5-$HT_{2A}$** ***antagonist***.
  - **Risperidone** & **Olanzapine**; **5-$HT_{2A}$** ***antagonist*** > **$D_2$** ***antagonist***.
  - **Quetiapine**; **$D_2$** ***antagonist*** > **5-$HT_{2A}$** ***antagonist***.
- ***Differences in First-Generation*** (*Most Common Agents*);

| | Potency | M (*block*) | $H_1$ (*block*) | $\alpha_1$ (*block*) | EPS |
|---|---|---|---|---|---|
| Chlorpromazine | Low | ++++ | +++++ | +++++ | ++ |
| Thioridazine | Low | +++++ | ++++ | +++++ | + |
| Perphenazine | Int. | ++ | ++ | ++ | +++ |
| Loxapine | Int. | +++ | +++ | ++ | +++ |
| Fluphenazine | High | ++ | ++ | ++ | ++++ |
| Thiothixene | High | ++ | ++ | ++ | ++++ |
| Haloperidol | High | + | ++ | + | ++++ |

## Pharmacological Action

- The ***pharmacological action*** of **antipsychotic drugs** appear to reflect a ***blockade*** at **dopamine** and/or **serotonin receptors**.
- However, ***many*** of **these agents** also ***block*** **cholinergic**, **adrenergic**, and **histaminergic receptors**.

1) **Antipsychotic Effects**;

A) **Positive Symptoms**; ***All*** **antipsychotic drugs** can ***reduce*** **hallucinations** and **delusions** ***associated with*** **schizophrenia**, ***mainly*** by ***blocking*** **$D_2$ receptors** in the **mesolimbic system** of the brain.

B) **Negative Symptoms**; ***Not responsive*** to the **first-generation agents**, but ***many*** **second-generation agents**, such as **Clozapine**, may be effective.

C) **Cognitive Symptoms**; ***Not responsive*** to ***all*** **antipsychotic drugs**.

2) **Antiemetic Effects**;

- ***Most*** of the **antipsychotic drugs** (*except* **Aripiprazole**) have **antiemetic effects**, ***mediated by*** **blocking $D_2$ receptors** of the **chemoreceptor trigger zone** (**CTZ**) of the medulla.

3) **Anticholinergic Effects**:

- ***Some*** of the **antipsychotics** (*particularly*; **Thioridazine**, **Chlorpromazine**, **Clozapine** and **Olanzapine**) produce **anticholinergic effects**.
- These effects ***include***; blurred vision, dry mouth (*except* **Clozapine**; ↑ salivation), confusion and constipation and urinary retention.
- The **anticholinergic effects** may actually ***assist*** in ***reducing*** the **risk** of **EPS** with these agents.

**4) Extrapyramidal Symptoms (EPS)**; (time and dose dependent)

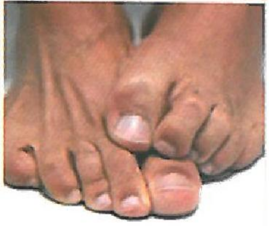
- EPS are ***drug-induced*** **movement disorders.**
- It ***can*** **occur** with ***both*** **acute** and **chronic treatment**.
- ***Blocking*** of **dopamine receptors** in the **nigrostriatal pathway** ***may cause*** **unwanted movement symptoms** (due to imbalance between ACh "excitatory" & Dopamine "Inhibitory").
- The **second-generation agents** ***exhibit*** a ***lower*** **incidence** of **EPS**.
- ***Conditions*** of **EPS**;

### A Dystonia

- **Dystonia** is a sustained muscle contractions or abnormal postures.
- **Muscular spasms** ***of***; neck, jaw, back, extremities, eyes (oculogyric crisis), throat (laryngospasm) and tongue.
- ***Highest risk*** in **young men**.
- This is also ***treated with*** **anticholinergic.**

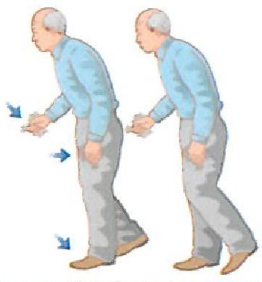
### B Akathisia

- **Akathisia**; A ***feeling*** of **internal motor restlessness** that can ***present*** as **tension**, **nervousness**, or **anxiety** (inability to stay still or calm).
- ***Treatments***;
  - ***Reducing*** the **antipsychotic** ***dose*** or ***switching*** to an **agent** with a ***lower incidence*** of Akathisia are the best options.
  - **β-blockers** (***lipophilic***) ***such as*** **Propranolol** and **Nadolol** are ***effective*** and are the agents of choice.
  - It poorly responds to anticholinergic.



### C Pseudoparkinsonism (Parkinson-like Symptoms)

- Parkinson-like symptoms ***such as***; bradykinesia, rigidity, tremor or akinesia.
- ***Greater risk*** in the elderly.
- It is ***usually*** **responsive** to **anticholinergic** agents such as **Diphenhydramine**, **Trihexyphenidyl** and **Benztropine**.



### D Tardive Dyskinesia

- ***Characterized by***; abnormal involuntary movements that occur with long-term antipsychotic therapy.
- It ***usually involves*** the **orofacial muscles** and is ***often*** **insidious.**
- If **treated** ***early***, it can be **reversible**, ***continued*** **drug exposure**, ***particularly*** at **high doses**, it is often **irreversible**.

- **Symptoms** may ***decrease*** with ***lowering*** the **dose** of antipsychotic or ***switching*** to an agent that is associated with less tardive dyskinesia (**Clozapine** has ***not been associated*** with tardive dyskinesia).
- **Anticholinergic agents** ***should not be given*** to treat tardive dyskinesia and ***may*** actually **worsen** the symptoms.

Pharmacological
Action

## Pharmacological Action

5) **Antiadrenergic Effects**;

- ***Blockade*** of **α-adrenergic receptors** cause **orthostatic hypotension** and **light-headedness** (***common*** in **older** and **dehydrated patients**).

6) **Antihistamine Effects**;

- **Sedation** occurs with drugs that are ***potent antagonists*** of the $H_1$ **receptor** (**Chlorpromazine**, **Olanzapine**, **Quetiapine** & **Clozapine**).

7) **Neuroleptic Malignant Syndrome** (NMS);

- This is ***another*** **serious complication** ***after*** **EPS**.
- It *occurs* with ***all agents*** but ***more common*** with **high-potency drugs**.
- ***Symptoms***; agitation, confusion, consciousness disturbance, fever, tachycardia, unstable blood pressure and sweating.
- Its **mortality rate** is ***high*** (*should be taken seriously*).
- ***Treatments***;
    - ***Discontinue*** the **drug** and give ***supportive therapy***, including **fluids** and **cooling**.
    - **Bromocriptine** (dopamine agonist) and **Dantrolene** (direct skeletal muscle relaxant) may be helpful.

8) **Endocrine Effects**;

- **Dopamine *inhibits* prolactin hormone** from pituitary.
- **Dopamine antagonists** can ***increase*** **prolactin** concentrations, can cause **hyperprolactinemia**;
    - ***In female***; Menstrual disturbance (**amenorrhea**) & **galactorrhea**.
    - ***In male***; **Gynecomastia** and **impotence** (erectile dysfunction).

## Therapeutic Uses

A) **Psychiatric Indications**;

- **Schizophrenia**; is the ***primary*** **indication** for antipsychotic agents.
- **Psychotic bipolar disorder** (**BP-I**), **psychotic depression** and **treatment-resistant depression**; **Chlorpromazine**, **Aripiprazole**, **Olanzapine**, **Quetiapine**, **Risperidone** & **Ziprasidone** are ***approved*** by the FDA for **treatment** of the **manic phase** of **bipolar disorder**.
- **Schizoaffective disorders**; characteristics of both **schizophrenia** and **affective disorders** (depression, bipolar disorder & anxiety disorder).
- **Tourette's syndrome** and ***disturbed behavior*** in patients with **Alzheimer's disease**.

B) **Non-psychiatric Indications**;

- **Prevention of nausea and vomiting**; ***most*** of ***older*** **typical antipsychotic drugs** (***except*** **Thioridazine**) have a ***strong*** **antiemetic effect**, **Prochlorperazine** used as antiemetic (see later).
- **Neuroleptanalgesia in medical procedure**; **Droperidol** (Butyrophenone, typical antipsychotic) is **used** in ***combination*** with **Fentanyl** (opioid) in **neuroleptanalgesia** (state of sedation and pain control induced for a medical procedure), (see page no. 380)

## Dose

| *Most Common* | Minim Effective Dose (mg) | Usual Daily Doses (mg) |
|---|---|---|
| **Chlorpromazine** | 100 | 100-1000 |
| **Fluphenazine** | 2 | 2-60 |
| **Haloperidol** | 2 | 2-60 |
| **Clozapine** | 50 | 300-600 |
| **Aripiprazole** | 10 | 10-30 |
| **Olanzapine** | 5 | 10-30 |
| **Quetiapine** | 150 | 150-800 |
| **Risperidone** | 4 | 4-16 |
| **Ziprasidone** | 40 | 80-160 |

## Side Effects

- Adverse effects of the antipsychotic drugs can occur in practically all patients and are significant in about 80%.

A) *Serious Side Effects*;

1) **Extrapyramidal Side Effects (EPSE)**; *see previous pages.*
2) **Neuroleptic Malignant Syndrome (NMS)**; *see previous pages.*

B) *General Side Effects*;

1) **Sedation and drowsiness**;
    - *Due to* **antihistaminic effects**, *usually* during the **first few weeks** of treatment, *particularly* with **Chlorpromazine**, **Olanzapine**, **Quetiapine** & **Clozapine**.
2) **Antimuscarinic Side Effects**;
    - *Particularly*; **Thioridazine**, **Chlorpromazine**, **Clozapine** and **Olanzapine** may produce blurred vision, dry mouth (except **Clozapine**), urinary retention and constipation.
3) **Orthostatic Hypotension and light-headedness**;
    - *Due to* **block α-adrenergic receptors**.
4) **Hyperprolactinemia**;
    - ***In female***; Menstrual disturbance (**amenorrhea**) & **galactorrhea**.
    - ***In male***; **Gynecomastia** and **impotence** (erectile dysfunction).
5) **Sexual Dysfunction**:
    - ***Erectile problems*** occur in 23-54% of men.
    - ***Loss*** of **libido** may occur in **men** and **women**.
6) **Weight Gain**;
    - This occurs in up to 40% of patients, with ***low-potency agents*** having ***higher*** **risk**.
    - Weight gain may occur because of ***actions*** at **histamine** or **serotonin receptors**.
7) **Risk of Venous thromboembolism (VTE)**;
    - **Recent study** ***showed*** the **antipsychotic drugs** (FGAs and SGAs) were associated with ***greater risk*** of **deep VTE** or **pulmonary embolism**.

C) *Specific Side Effects for Typical Antipsychotics*;

- ***Low-potency agents*** (**Thioridazine** and **Chlorpromazine**) can cause **pigmentary** ***deposits*** on the **retina** and **corneal opacity**.
- ***Many*** of the **typical agents** (**Thioridazine**, **Pimozide**, and ***IV*** **Haloperidol**) can cause ***serious*** **ECG changes** (e.g., **QT interval** ***prolongation***), these changes can ***lead to*** **arrhythmias** and **death**.

D) *Specific Side Effects for Atypical Antipsychotics*;

### Clozapine (Clozaril®)

- **Clozapine** ***Serious Side Effects***:
    - **Agranulocytosis**;
        - ***Reduction*** in **white blood cell** ***count***, and it ***increases*** the ***risk*** of **serious** or **fatal infections**.
        - It is occurs ***about*** **1-2%** and is ***highest*** during the ***first*** **4-6 months of therapy**.
        - It is ***contraindicated*** if the white blood cell count is ***less than*** 3500 cells/mm$^3$.
        - Patients ***must be*** **enrolled** in a **Clozaril registry program**, which ***monitors*** **neutrophil** and **white blood cell** ***counts***.
    - ***Black box warnings***; **seizures** (at higher doses) and **myocarditis**, **orthostatic hypotension** and **respiratory arrest**.

| SGAs | Metabolic Effects | | | Cardiac Effects | Sedation | Other (or Notes) (dose dependent) |
|---|---|---|---|---|---|---|
| | Weight gain | Diabetes | Dyslipidemia | | | |
| **Clozapine** | Highest | Yes | High | OH, prolonged QT & tachycardia | High | Agranulocytosis and Seizures |
| **Aripiprazole** | Little to none | No | Little to none | None | Low | ↓ prolactin and akathisia |
| **Olanzapine** | Highest | Yes | High | None | High | - |
| **Asenapine** | Little to none | Little to none | Little to none | OH, prolonged QT | Low | Akathisia |
| **Iloperidone** | Moderate | Low | Low | OH, prolonged QT | Low | - |
| **Lurasidone** | Low | Low | Low to none | None | Moderate | Akathisia and Parkinson-like |
| **Paliperidone** | Low | Low | None | Prolonged QT | Low | Hyperprolactinemia and EPS |
| **Quetiapine** | Moderate | Moderate | Moderate | OH | High | ***Drug of choice*** **in Parkinson's** |
| **Risperidone** | Moderate | Moderate | Less | OH | Low | Hyperprolactinemia and EPS |
| **Ziprasidone** | Little | No | Less | (↑) Prolonged QT | Low | ECG monitoring |

OH = Orthostatic Hypotension "Table from ACCP Updates in Therapeutics 2015"

**FDA Warning**

- ***Most*** **of antipsychotics** *may* ***lower*** **the seizure threshold** and ***should be*** **used** ***cautiously*** in **patients** with **seizure disorders** or **those** with an ***increased*** **risk for seizures**, such as **withdrawal from alcohol.**
- ***Most*** **of antipsychotics** also carry the **black box warning** of ***increased risk*** for **mortality** when used in **elderly patients** ***with*** **dementia related psychosis.**

## ➢ Therapy Duration:-

- **Relapse rates** are ***more than*** **50%** ***during*** the **first year**.
- Patients who have had ***two*** or ***more*** **psychotic episodes** ***secondary*** to **schizophrenia** should receive **maintenance therapy** for ***at least*** **5** years.
- **Long-term therapy** *should include* ***monitoring*** for **metabolic complications** such as **diabetes, weight gain** and **lipid abnormalities**.

## ➢ Adjunctive Therapy:-

1) **Lithium**: This agent may ***augment*** **antipsychotic action.**
2) **Anticonvulsants** (**Carbamazepine** and **Valproic acid**): These agents may ***augment*** **antipsychotics**, may be ***useful*** in patients with **agitated** or **violent behaviour**.
3) **Benzodiazepines**: may be ***useful*** during the ***acute phase*** for **agitation** or **anxiety**, these drugs ***must be*** **used** ***with caution***, because the schizophrenic patients are high risk of substance abuse.

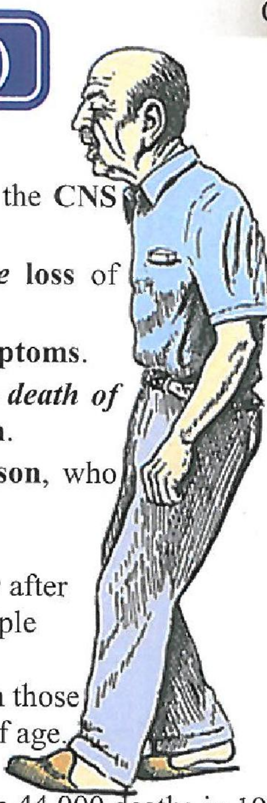
# Psychosocial Treatments

- ***Once*** **psychosis** ***recedes***, **psychological** and **social** (**psychosocial**) therapies are ***important.***
- ***These may include***:

- **Individual therapy**; learning to cope with stress and identify early warning signs of relapse can help people with schizophrenia manage their illness.
- **Social skills training**; this focuses on improving communication and social interactions.
- **Family therapy**; this provides support and education to families dealing with schizophrenia.
- **Vocational rehabilitation and supported employment**; this focuses on helping people with schizophrenia prepare for, find and keep jobs.

- ***N.B.***; April 29, 2016; The U.S. **FDA** ***approved*** **Pimavanserin** (Nuplazid®) tablets, the ***first drug*** approved to treat **hallucinations** and **delusions** ***associated with*** psychosis experienced by some people with **Parkinson's disease.**

# Parkinson's Disease (PD)



## ➢ Overview:-

- **Parkinson's Disease (PD)**; is a ***neurodegenerative disease*** of the **CNS** mainly affecting the **motor system.**
- **Neurodegeneration**; is the umbrella term for the ***progressive*** **loss** of **structure** or **function** of neurons, ***including*** **death of neurons.**
- **Parkinsonism (Parkinsonian)**; is a **term *used for*** a **motor symptoms.**
- The **motor symptoms** of **Parkinson's disease** ***result from*** the ***death of*** **dopamine-generating cells** in the **substantia nigra** in **midbrain.**
- The disease is ***named*** after the English doctor **James Parkinson**, who published the ***first detailed*** **description** in 1817.
- ***Prevalence***;
  - PD is the ***second most common*** **neurodegenerative disorder** after **Alzheimer's disease** and affects approximately **7 million** people globally and **1 million** people in the **United States.**
  - PD is ***more common*** in the **elderly** and rates rises from **1%** in those ***over*** **60 years** of age to **4%** of the population ***over*** **80 years** of age.
  - **Onset**; *usually* ***between*** **40-70 years of age** (***mean age***; 60).
  - In 2013 PD resulted in about 103,000 deaths globally, up from 44,000 deaths in 1990.

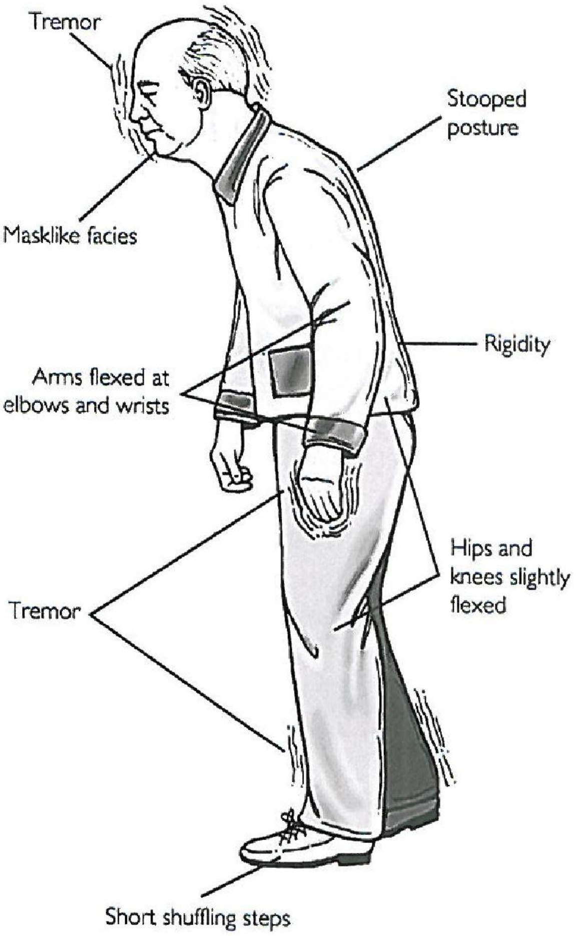
## ➢ Signs (or Symptoms):-

- **Cardinal Signs**;

**1) Tremor***;
- It is the ***most common*** symptom.
- About **30%** ***not*** have tremor ***during first stages*** of the disease, **but** appearing later.
- **Form of tremors**; usually, **REST TREMOR**; appear maximum at is at rest (***free*** limbs) and disappearing usually with voluntary movement and sleep.
- **Onset**; typically appears in only a single arm or leg, **but** becoming bilateral later.
- **Frequency**; between 4-6 hertz (one per second).

**2) Akinesia/Hypokinesia (Bradykinesia)***;
- **Akinesia**; ***without*** motion, **Hypokinesia (Bradykinesia);** ***slow*** (***decrease***) motion.
- ***Over time***, PD may ***reduce*** **ability to move** and ***slow*** **movement**, making simple tasks difficult and time-consuming.
- ***Movement***; ***short*** **steps** with **crawling sensations.**

**3) Rigidity***;
- **Muscle stiffness** to **movement** *caused by* ***increase*** **muscle tone** and *may occur* in ***any*** **part** of the body.
- **Rigidity** may be *associated with* **pain.**



- **In late stages**; rigidity may affects the **whole body** and ***reduces*** the **ability to move.**

**4) Posture (Gait) Instability**;
- ***Impaired*** **balance** and ***frequent*** **falls** and ***may lead to*** secondary **bone fractures.**
- ***Typically*** in the **late stages** of the disease.

- **Secondary Signs**;
  1) **Cognitive Dysfunction**; the most common cognitive deficit is executive dysfunction.
  2) **Autonomic Dysfunction**; such as, orthostatic hypotension, oily skin and excessive sweating, urinary incontinence, sexual function disturbance and vision abnormalities.
  3) **Speech Disturbances**; speech may become softer, and less clear when moving around.
  4) **Micrographia** (**Handwriting**); it may become hard to write, and writing may appear small.
  5) **Masked Facies** (**Hypomimia**); reduced degree of facial expression.

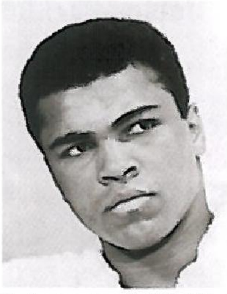
### ➢ Clinical Diagnosis:-

- Clinical diagnosis requires the *presence* of 2 of 3 **cardinal signs**;

  1) Resting tremor. 2) Rigidity. 3) Bradykinesia.

### ➢ Famous People Diagnosed with Parkinson's Disease:-

**Adolf Hitler (1889-1945)**



**Muhammad Ali Clay (1942-2016)**

**Yasser Arafat (1929-2004)**

**Pope John Paul II (1978-2005)**

### ➢ Causes:-

- PD in ***most people*** is **idiopathic** (unknown cause).
- ***Most of cases*** are due to a ***combination of*** **genetic** and **environmental factors**.
- *Currently*; about **10%** of **cases** ***due to*** **genetic factors**.
- **Environmental Factors**; Exposure to certain toxins or environmental factors may increase the risk Parkinson's disease;
  - **Pesticides Exposure**;
    - ***Studies found*** that exposure to pesticides may increase the risk for PD, ranging from 33%-80%.
    - ***Implicated agents***; *primarily* **Chlorpyrifos** and **organochlorines** and **pesticides**; such as **Rotenone** or **Paraquat** and **herbicides**.
  - **MPTP Exposure**;
    - ***Several* individuals** were identified who developed parkinsonism after **self-injection** of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MPTP (**street- *abuse* drug**).
    - MPTP is a **neurotoxin**, has been identified in underground laboratory preparations of a ***potent analogue*** of **Meperidine** (an Opioid).
  - **Heavy metals exposure**; risk factor, through possible accumulation in the substantia nigra.
- **Oxidation Hypothesis**;
  - Dopamine oxidation by MAO leads to the formation of hydrogen peroxide (free radical), normally cleared rapidly by glutathione, but if hydrogen peroxide is not cleared adequately, cause cell damage and may develop of Parkinson disease.
- **Alpha-synuclein Aggregation**;
  - **Genetic** (*SNCA gene*) ***abnormally*** aggregation of **alpha-synuclein** (the major component of **Lewy bodies** and **Lewy neurites**) ***play*** a **central role** in the **pathogenesis** of **PD**.
  - **Lewy bodies** is the ***main*** **microscopic markers** of **Parkinson's disease**.

### ➢ Pathophysiology:-

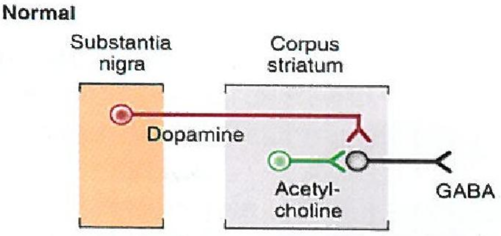
1) *Loss* of **dopaminergic neurons** in the **substantia nigra**.
2) *Presence* of **Lewy bodies** and **Lewy neurites**.

### ➢ Prevention:-

- **Exercise**; exercise in middle age reduces the risk of Parkinson's disease later in life.
- **Caffeine**; higher caffeine intake was associated with lower risk of Parkinson disease.
- **Antioxidants** have been proposed to protect against Parkinson disease.

## ➢ Managements:-

- There is *no treatment* has been shown to *prevent progression* of **PD.**
- **Treatments** is **based on symptoms.**
- *Antiparkinsonian Agents*;
  1) **Levodopa/Carbidopa.**
  2) **Dopamine Receptor Agonists.**
  3) **MAO-B Inhibitors.**
  4) **COMT Inhibitors.**
  5) **Other Agents.**


Normal
Substantia nigra
Corpus striatum
Dopamine
Acetyl-choline
GABA

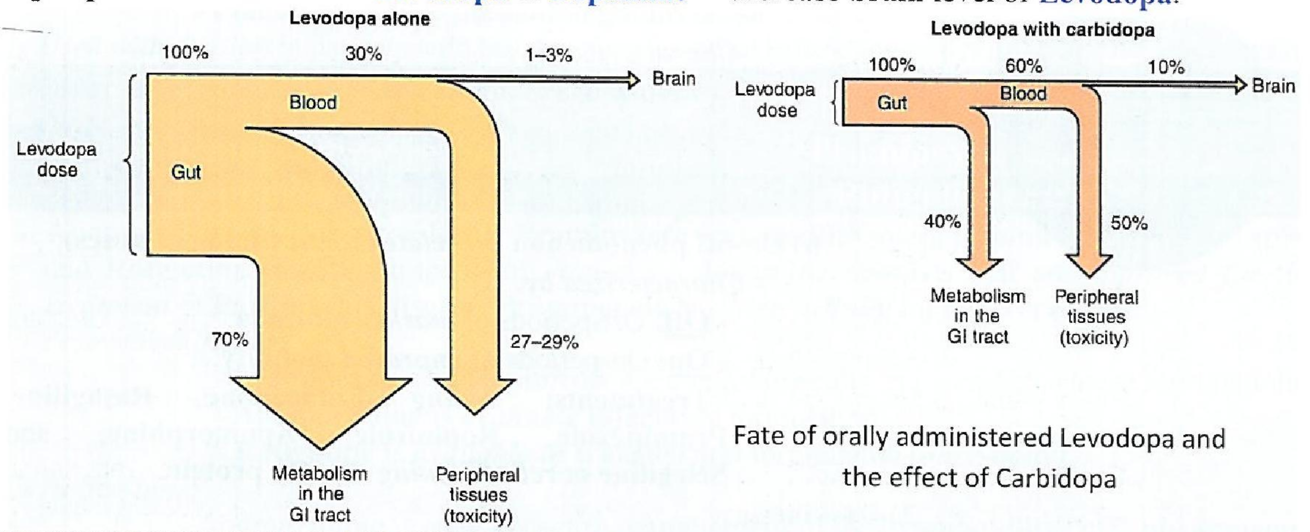
**Dopamine-ACh Balance**; Dopaminergic neurons (red) originating in the substantia nigra normally inhibit the GABAergic output from the striatum, whereas cholinergic neurons (green) exert an excitatory effect.

# Antiparkinsonian Drugs

## I) Levodopa (L-dopa)

### Levodopa/Carbidopa (Sinemet®) (Parcopa®)

- **Dopamine** ***can't*** be **given** in the **treatment** of **PD** as it ***doesn't*** **penetrate** the **BBB.**
- **Dopa** is the **amino acid** ***precursor*** of **Dopamine.**
- **Levodopa** (**L-dopa**) [LEE-voe-DOE-pa] is the ***levorotatory stereoisomer*** of **dopa.**
- **Levodopa** is ***metabolized*** to **Dopamine** by the ***dopa-decarboxylase*** **enzyme.**
- ***More than*** **95%** of **Levodopa** is ***metabolized*** **outside** the **brain** by **peripheral** ***dopa-decarboxylase.***
- ***Only*** about **1-3%** of **Levodopa** ***enters*** the **brain.**
- **Levodopa** is ***combined*** with **peripheral** ***dopa-decarboxylase*** **inhibitors (DDCI); Carbidopa** [KAR-bi-DOE-pa] and **Benserazide** [ben-SER-a-zide] (doesn't cross BBB) ⇨ ***Prevents some*** of the **peripheral conversion** of **Levodopa** to **Dopamine** ⇨ ***increase*** **brain level** of **Levodopa.**


Levodopa alone
100%
30%
1–3%
Brain
Blood
Levodopa dose
Gut
70%
27–29%
Metabolism in the GI tract
Peripheral tissues (toxicity)
Levodopa with carbidopa
100%
60%
10%
Brain
Levodopa dose
Gut
Blood
40%
50%
Metabolism in the GI tract
Peripheral tissues (toxicity)

Fate of orally administered Levodopa and the effect of Carbidopa

**Pharmaco Kinetics**

- **Levodopa** is ***rapidly*** **absorbed** from the **small intestine.**
- **Absorption** ***depends on*** **gastric emptying rate** & **pH of gastric contents.**
- **Food** ***delays*** the **absorption** of **Levodopa.**
- **Amino acids** ***from*** **ingested food** (high-protein diets) can ***compete*** with **Levodopa** for **absorption** and for **transport** ***to the*** **brain.**
- ***Plasma Peak***; **1-2 hours** after an oral dose.
- ***Half-life***; *usually*, **1-3 hours.**

**Efficacy**

- ***Greatest effect*** on **bradykinesia** and **rigidity**
- ***Less effect*** on **tremor** (*controlled by* **Propranolol**) & **postural instability.**
- ***Improvement*** in **disability** and possibly **mortality.**

# III) Monoamine Oxidase-B (MAO-B) Inhibitors

| **Selegiline** (Eldepryl®) | **Rasagiline** (Azilect®) |
|---|---|

- *Two types* of **Monoamine Oxidase** (**MAO**);
  - **Monoamine Oxidase-A** (**MAO-A**); ***metabolizes*** **Norepinephrine**, **Serotonin** and **Dopamine**.
  - **Monoamine Oxidase-B** (**MAO-B**); ***metabolizes*** **Dopamine** ***selectively***.
- **Selegiline** [seh-LEDGE-ah-leen], ***also called*** **Deprenyl** [DE-pre-nill], ***selectively inhibits*** **MAO-B** at **low** to **moderate doses**, at **high doses** (***greater than*** 10 mg/day) it ***loses*** its **selectivity**.
- **Rasagiline** [ra-SAgi-leen], an ***irreversible*** and ***selective inhibitor*** of **MAO-B** at ***all doses***, has **five times** the ***potency*** of **Selegiline**.
- ***Unlike*** **non-selective MAOIs**, has ***little*** **potential** for **hypertensive crises**, (***but***, **Selegiline** at ***high doses*** has a ***risk for*** **severe hypertension**.
- ***Formulations***;
  - **Selegiline**; **tablets, orally dissolving tablets** and **patches**. The patches (Emsam®) are FDA approved ***only for*** **depression**.
  - **Rasagiline**; ***once daily*** **tablets**.
- ***Dose***;
  - **Selegiline**;
    - **Tablets**; 5 mg orally twice daily (morning and noon).
    - **Disintegrating tablets**; 1.25-2.5 mg/day.
  - **Rasagiline**; 0.5-1 mg/day orally.
- **Selegiline** is ***metabolized to*** **amphetamine-like substances**, may produce insomnia if the drug is administered at night, (**Rasagiline** is not metabolized to an amphetamine-like substance).
- **Selegiline** may **administered** ***with*** **Levodopa**, it ***enhances*** the **actions** of **Levodopa** and substantially ***reduces*** the **required dose**.
- ***Common Side Effects***; **Nausea**, **hallucinations** and **orthostatic hypotension** (**insomnia** ***only with*** **Selegiline**).
- ***Drug Interactions***;
  - **Selegiline**; ***with*** **Meperidine** ⇨ ***increase risk*** of **serotonin syndrome**.
  - **Rasagiline**; ***with*** **Tramadol**, **Methadone**, **Dextromethorphan**, **Sympathomimetics**, **Fluoxetine**, or **Fluvoxamine** ⇨ ***increase risk*** of **serotonin syndrome**.
    - **Ciprofloxacin** ↑ **Rasagiline** **concentration** (through **CYP1A2** inhibition).

# IV) Catechol-O-Methyltransferase (COMT) Inhibitors

| **Tolcapone** (Tasmar®) | **Entacapone** (Comtan®) |
|---|---|

- ***Normally***, the ***methylation*** of **Levodopa** by **catechol-O-methyltransferase** (**COMT**) to **3-O-methyldopa** (**3-OMD**) is a ***minor*** **pathway** for **levodopa metabolism**.
- ***When*** **peripheral** ***dopa-decarboxylase*** is inhibited by **Carbidopa** ⇨ a ***compensatory*** **mechanism** of **Levodopa** **metabolism** is **activated** ***through*** **COMT** ⇨ ***increases*** **plasma levels** of **3-OMD**.
- ***Elevated*** **levels** of **3-OMD** ⇨ ***associated with*** a **poor therapeutic response** to **levodopa** (It is ***competes*** with levodopa for **active transport** into the CNS).
- **Tolcapone** [TOLE-ka-pone] and **Entacapone** [en-TAK-a-pone] are ***selectively*** and ***reversibly*** **inhibit COMT**.
- **Tolcapone** has both **central & peripheral** ***effects***, whereas the effect of **Entacapone** is **peripheral**.
- **Tolcapone** is ***severely*** **widely restricted** ***because*** of **hepatotoxicity** (**Entacapone** has ***largely replaced*** **Tolcapone**).
- **COMT inhibitors** ***reduce*** the **symptoms** of **fluctuations response** in ***patients*** used **Levodopa/Carbidopa**.
- ***Side effects***; **Dyskinesia**, **nausea**, **diarrhea**, **urine discoloration** (orange) and **hallucinations**.
- **Stalevo®**; Consists of a ***combination*** of **Levodopa** /**Carbidopa**/**Entacapone**. It is available in ***three*** **strengths**: Stalevo® 50 (50/12.5/200 mg), Stalevo® 100 (100/25/200 mg) and Stalevo® 150 (150/37.5/200 mg).

## V) Other Agents

### Anticholinergic Agents

**Benztropine** (Cogentin®) | **Trihexyphenidyl** (Parkinol®) | **Biperiden** (Akineton®)

**Procyclidine** (Kemadrin®) | **Orphenadrine** (Norflex®)

- ***Blockage*** of **cholinergic transmission** in the brain, **helps** to ***correct*** the **imbalance** in the **Dopamine/Acetylcholine ratio**.
- **Anticholinergic drugs** were the ***first*** **pharmacological agents** used in the ***treatment*** of **Parkinson's disease** (**Orphenadrine** is the first agents used in 1940s).
- **These agents** may ***improve*** **tremor & rigidity** ***but*** have ***little effect*** on **bradykinesia**.
- **Benztropine** [BENZ-troe-peen], **Trihexyphenidyl** [tri-hex-ee-FENi-dill] and **Biperiden** [bye-PER-i-den] are ***more common*** **antimuscarinic agents** ***used in*** **Parkinson's disease**.
    - ***Dose***;
        - **Trihexyphenidyl**; ***initial dose*** 0.5 mg orally twice daily, ***maintenance*** 6- 10 mg/day.
        - **Benztropine**; ***initial dose*** 0.5 mg orally twice daily, ***maintenance*** 1-6 mg/day.
        - **Biperiden**; **2 mg** orally 3 to 4 times a day.
- **Procyclidine** [pro-SYE-kli-deen] ***may*** use in **Parkinson's disease**.
- **Orphenadrine** [ore-FEN-uh-dreen] is a ***derivative*** of the ***first-generation*** **antihistamine Diphenhydramine** and has effects to ***block*** **muscarinic receptors**, ***now rarely*** **used in Parkinson's disease** (it is particularly toxic in overdose), ***but*** **used** in ***acute*** **painful musculoskeletal conditions**.
- ***Common Side Effects***; **Confusion, dry mouth, dry eyes, urinary retention** and **constipation**.

### Other Agent

**Amantadine** (Symmetrel®)

- **Amantadine** [a-MAN-ta-deen] is an antiviral agent, was ***by chance*** found to have ***Antiparkinsonism properties***.
- ***Mechanism of action*** in parkinsonism is unclear, but it may ***potentiate*** **dopaminergic function** by influencing the synthesis, release or reuptake of dopamine. ***Current*** **evidence supports** ***action*** at **NMDA receptors**.
- It has ***symptomatic*** **benefits** and may ***reduce*** **dyskinesia** caused by **Levodopa** or **dopamine agonists**.
- ***Dose***; 100 mg orally 2-3 times daily (***caution*** in **renal dysfunction**).
- ***Side effects***; **Dizziness, insomnia, anxiety, livedo reticularis** (skin consists of a mottled reticulated vascular pattern), **nausea** and **nightmares**.

## Surgical Procedures

**A) Deep Brain Stimulation (DBS)**;

- In DBS, surgeons implant electrodes into a specific part of the brain. FDA approved DBS as a treatment for Parkinson's disease in 2002.
- DBS is used in people with advanced Parkinson's disease who have unstable medication responses.
- DBS can stabilize medication fluctuations, reduce dyskinesia, reduce tremor, reduce rigidity and improve slowing of movement.

**B) Thalamotomy**; A selected portion of the thalamus (control tremor) is destroyed (ablated).

**C) Pallidotomy**; Ablation of structures in the globus pallidus.

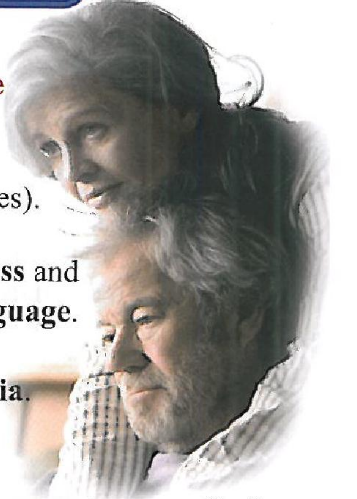
**D) Trophic Factors**; Glial-derived nerve growth factor and neurturin have been delivered directly to the striatum or substantia nigra (*experimental*).

**E) Fetal Transplants**; Transplantation of dopaminergic tissue from a fetus to a patient striatum (*experimental*).

- ***N.B.***; **Physicians** may ***suggests*** **Parkinson's stretching exercises** to ***improve*** gait, balance, tremor, flexibility, grip strength and motor coordination.
- April 29, 2016; The U.S. FDA approved **Pimavanserin** (Nuplazid®) tablets, the first drug approved to treat **hallucinations** and **delusions** ***associated with*** psychosis experienced by some people with **Parkinson's disease**.

# Alzheimer's Disease (AD)

## ➢ Overview:-



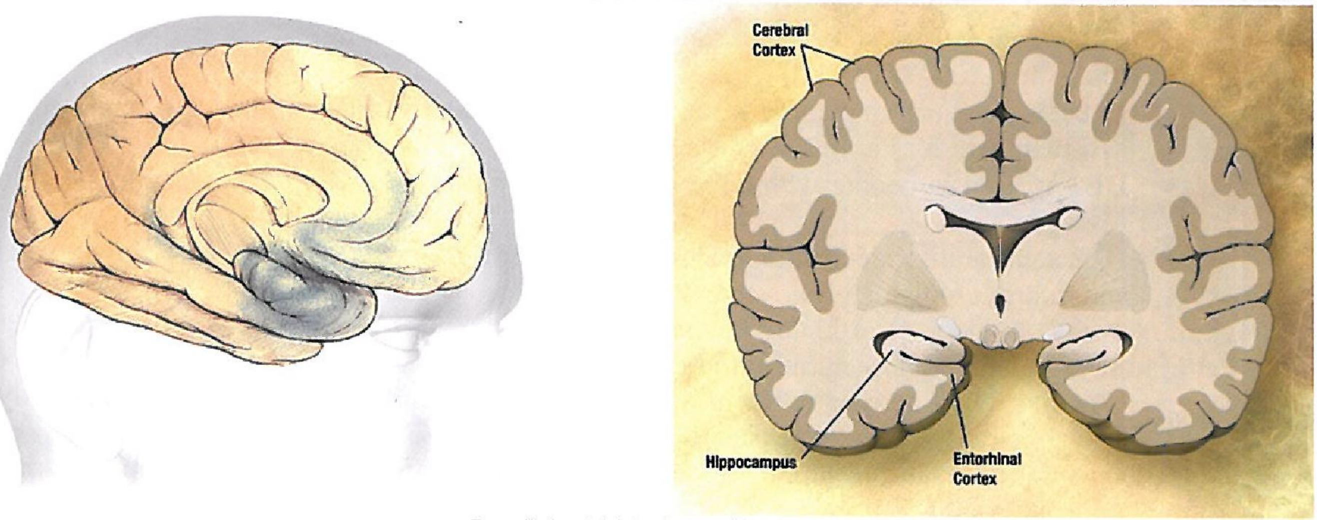
- **Alzheimer's disease**; is a ***slow progressive*** **neurodegenerative disease** that ***destroys*** **memory** and ***other*** **important mental functions.**
- It is the ***most common*** **type** ***of*** **dementia** (*about* 60-70% of cases).
- ***Dementia***;
  - It is a ***set*** of **symptoms** that can ***include*** **memory loss** and **difficulties** ***with*** **thinking, problem-solving** or **language.**
  - Other ***common types*** include **vascular dementia, Lewy body dementia** and **frontotemporal dementia.**
  - The **DSM-5** ***replaces*** the term "**dementia**" with "**major** or **mild neurocognitive disorder**".
- ***No treatments*** **stop** or **reverse** its **progression**, though some ***may temporarily improve*** **symptoms.**
- It was ***first*** **described** and **named** by **German psychiatrist** and pathologist **Alois Alzheimer** in **1906.**
- ***Prevalence*** (*According* to **WHO Dementia Fact Sheet 2015**);
  - Worldwide, **47.5 million** people have **dementia** and there are **7.7 million** ***new*** **cases every year**, and is projected to increase to 75.6 million by 2030. The number of cases of dementia are estimated to more than triple by 2050.
  - **Alzheimer's disease** (**AD**) is the ***most common*** **cause** of **dementia** and may contribute to **60-70%** of **cases.**
  - **AD** affects an estimated **5.3 million** people in the **United States.**
  - In **US** AD was the **sixth** ***leading*** cause of **death** in **2015.**
  - In 2010, the ***total global*** **societal costs** of dementia was estimated to be US$ 604 billion.

## ➢ Signs (or Symptoms):-

- **Stages of Alzheimer's Disease;**

### 1) Preclinical (Pre-dementia) Alzheimer Disease

- **Patients** ***may*** **appear** ***completely*** **normal.**
- ***Specific*** **regions** of the **brain** (e.g., entorhinal cortex, hippocampus) probably ***begin*** to be **affected 10-20 years** ***before*** any **visible symptoms** ***appear***, and it can be ***diagnosed by*** **newer imaging techniques.**

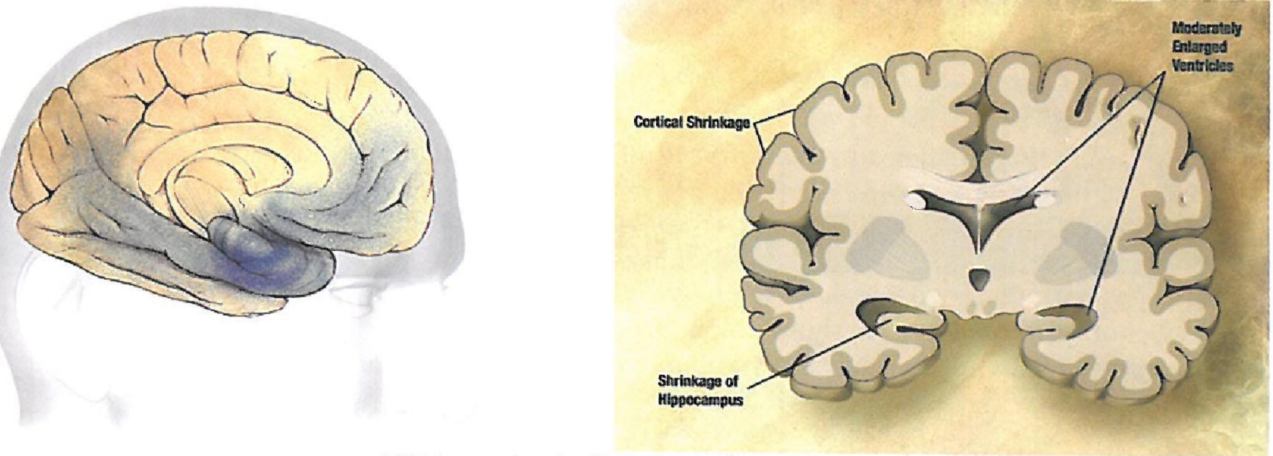


*Preclinical Alzheimer disease*

- The **first visible** ***sign*** is **Mild Cognitive Impairment** (**MCI**) and ***may appear*** in **preclinical stage;**
  - It is often found to be a ***transitional stage*** between **normal ageing** and **dementia.**
  - ***Predominant symptom*** of **MCI** is **memory loss.**

## 2) Mild Alzheimer Disease

- AD ***begins affect the*** **cerebral cortex**; **memory loss** ***continues*** & ***impairment*** of **cognitive functions.**
- The **clinical diagnosis** of **AD** is ***usually*** **made** ***during this*** **stage**. ***Signs*** can ***include the following***;
  - Memory loss for recent events [short-term memory (STM) loss].
  - Confusion about the location of familiar places.
  - Trouble remembering names when introduced to new people.
  - Taking longer to accomplish normal daily tasks.
  - Trouble handling money and paying bills.
  - Losing things or misplacing them in odd places.
  - Loss of spontaneity and sense of initiative.
  - Mood and personality changes; increased anxiety.



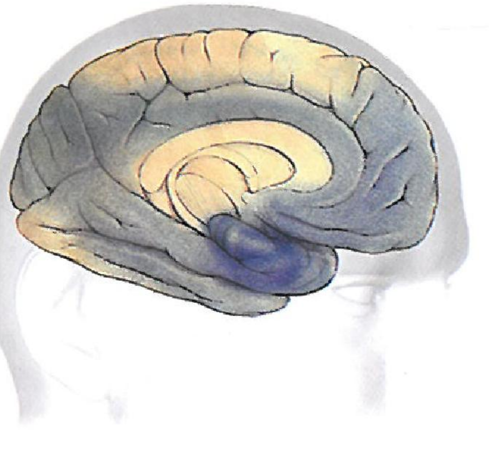
*Mild-to-moderate Alzheimer disease*

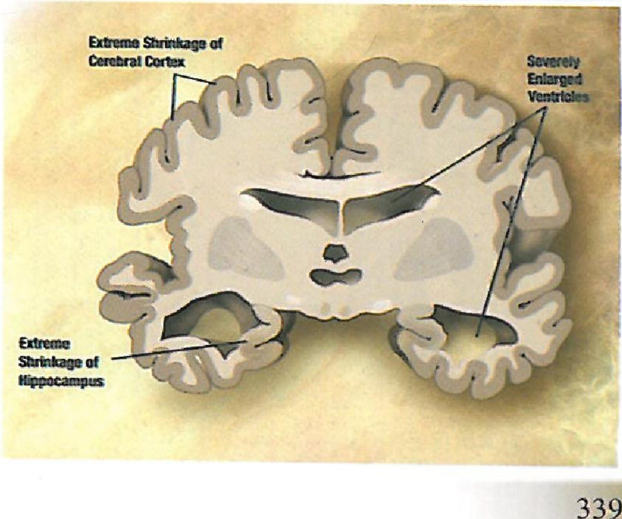
## 3) Moderate Alzheimer Disease

- ***By the time***, **damage** has ***spread*** further to the areas of the **cerebral cortex** that ***control*** **language**, **reasoning**, **sensory processing** and **conscious thought**.
- ***Signs*** of **moderate AD** can ***include the following***;
  - Increasing memory loss and confusion [long-term memory (LTM) loss].
  - Problems recognizing friends and family members.
  - Difficulty with language; problems with reading, writing, working with numbers.
  - Difficulty organizing thoughts and thinking logically.
  - Difficulty with some daily activities (need help with clothing, using the bathroom & other self-care).
  - Lose control of their bladder or bowels in some individuals.
  - Personality and behavioural changes; delusions or compulsive restlessness, agitation and anxiety.

## 4) Severe (Advanced) Alzheimer disease

- In the ***last stage***, **damages** are ***widespread*** throughout the brain and areas of the brain have atrophied.
- Patients cannot recognize family or communicate in any way.
- Completely dependent on others for care and vanish of all self-sense.
- Death is often the result of other illnesses, frequently pneumonia.




Extreme Shrinkage of Cerebral Cortex
Severely Enlarged Ventricles
Extreme Shrinkage of Hippocampus

## ➢ Causes/Pathophysiology:-

- The **causes** of ***most cases*** of **Alzheimer's** is ***still*** **unknown**, ***except*** in **some cases** (*less than 5%*) the causes is **genetics**.
- ***Several*** **hypotheses** exist *trying to* **explain** the **cause** of the **disease**;

### 1) Genetics

- This **genetic type** of the disease is ***also called***; **Familial Alzheimer's Disease (FAD)**.
- It is ***caused by*** a **mutation** in **one** of ***at least*** 3 **genes**: **Presenilin 1**, **Presenilin 2** and **Amyloid Precursor Protein (APP)**.
- **Mutations** in this **genes** ***increase*** the **production** of a **small protein** called **β-amyloid (Aβ)**, which is the ***main component*** of **senile plaque** (*see amyloid hypothesis*).

* In ***most cases*** of **Alzheimer's disease**, the ***environmental*** and ***genetic differences*** may ***act as*** **risk factors**;

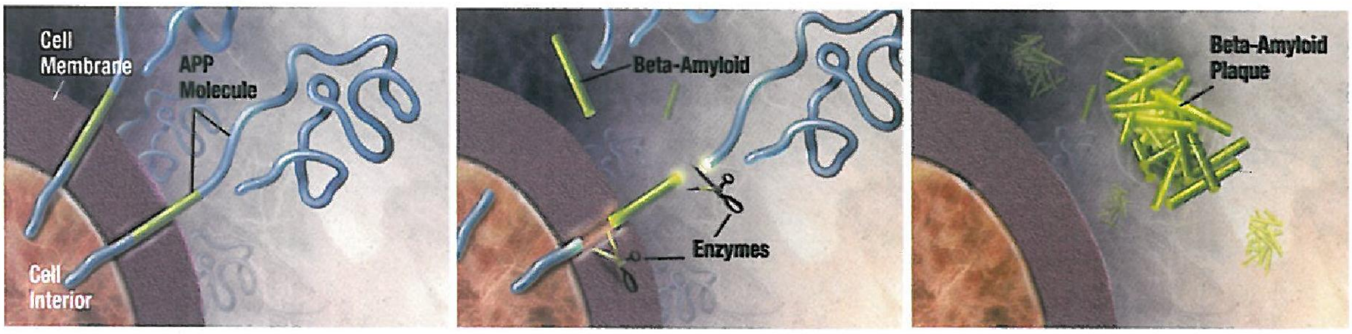
- The ***best known*** **genetic risk factor** is **Apolipoprotein E (APOE) gene** (found between 40% and 80% of people with AD).
- **APOE gene** helps in the ***synthesis*** of **Apolipoprotein E**, which is a **cholesterol** ***carrier*** in the brain, ***helping*** in **amyloid aggregation**.

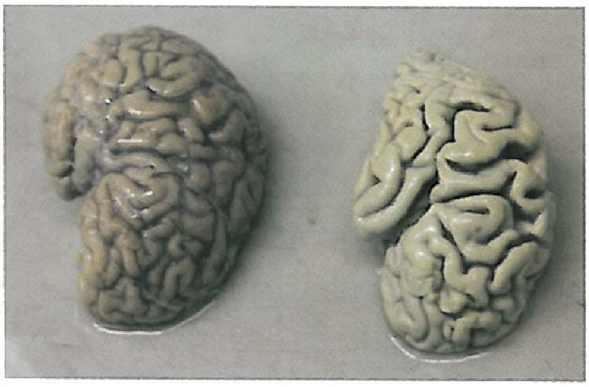
### 2) Cholinergic Hypothesis

- The ***oldest*** **hypothesis** on which ***most currently available*** **drug therapies** are ***based***.
- **Acetylcholine** ***needed to*** **pass signals** along ***from*** **cell** ***to*** **cell**.
- The **cholinergic hypothesis** has ***not maintained*** **widespread** ***supported***.

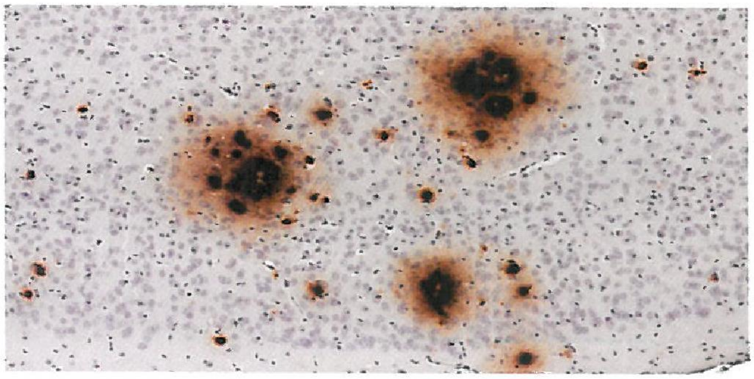
### 3) Amyloid Hypothesis

- *In 1991*; the **amyloid hypothesis** postulated that extracellular **β-amyloid** or **amyloid beta (Aβ) protein** ***deposits*** are the ***fundamental*** **cause** of the **disease**.
- **AD** has been ***identified as*** a **protein misfolding disease** *due to* the ***accumulation*** of ***abnormally folded*** **β-amyloid protein** in the brains of **Alzheimer's patients**.
- **Amyloid protein** is a sequencing of its amino acid chain and the cloning of the **gene** encoding its precursor protein (**Amyloid Beta Precursor; APP**).
- **Amyloid protein** is formed by enzymatic cleavage of **Amyloid Beta Precursor (APP)**.
- ***Over*** **aggregation** of **β-amyloid**, can ***blocks*** the normal transport of **electrical messages** between the neurons and ***may cause*** **cell death**.





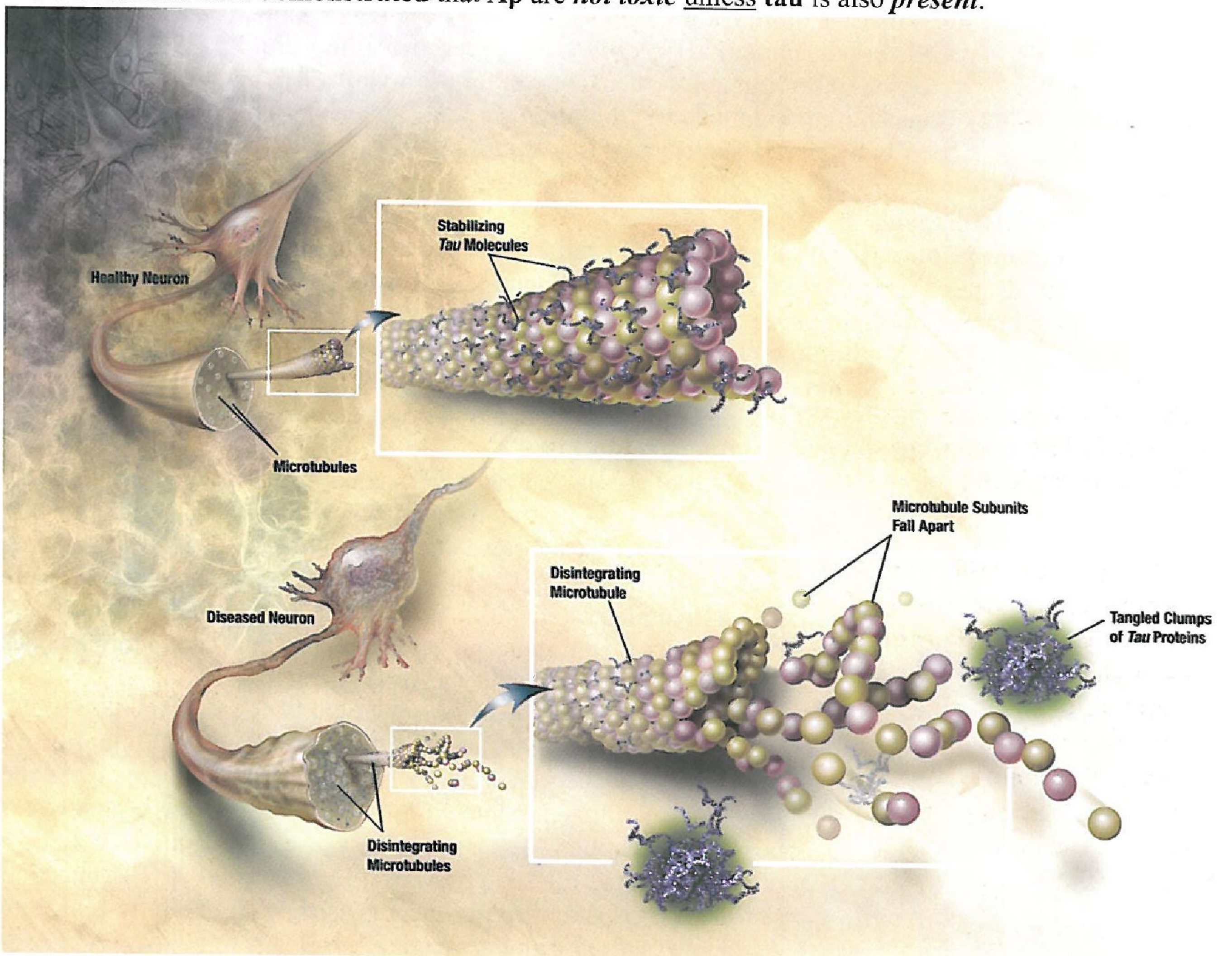
*Healthy brain – Alzheimer brain*



*Amyloid plaques under microscope*

# 4) Tau Hypothesis

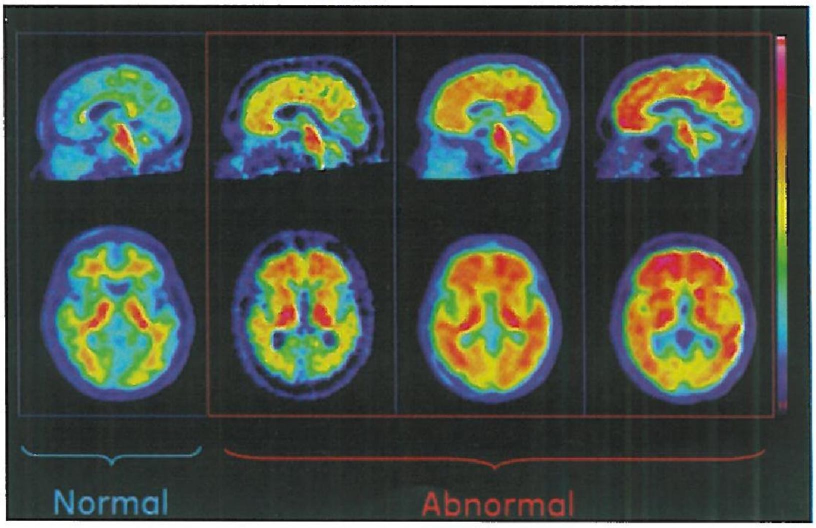
- **Tau protein** is a ***highly soluble*** **Microtubule-Associated Protein** (**MAP**).
- ***Excessive*** or ***abnormal*** **phosphorylation** of **tau protein** results in the ***transformation*** of normal adult **tau** into **PHF-tau** (paired helical filament) and **NFTs** (neurofibrillary tangles) ⇨ ***interacts*** with **tubulin** (tubulin *responsible for* ***stabilize*** **microtubule assembly**) ⇨ ***disintegration*** of **microtubules** in brain cells ⇨ **cell *death***.
- ***Some studies*** have **demonstrated** that **Aβ** are ***not toxic*** unless **tau** is also ***present***.


Stabilizing
*Tau* Molecules
Healthy Neuron
Microtubules
Microtubule Subunits
Fall Apart
Disintegrating
Microtubule
Tangled Clumps
of *Tau* Proteins
Diseased Neuron
Disintegrating
Microtubules

## ➤ Clinical Diagnosis:-

- **Alzheimer's disease** is ***usually*** diagnosed ***based on***;
  - Person's medical history.
  - History from family and friends.
  - Behavioural observations.
  - Biomarker tests.
  - Brain imaging.
- *In 2011*, the National Institute on Aging (NIA) and the Alzheimer's Association also proposed new guidelines for diagnosis (*visit*; www.alz.org).
- **Alzheimer's disease biomarkers**;
  1) **CSF-based biomarkers**; ***Analysis*** of **cerebrospinal fluid (CSF)** by ELISA (enzyme linked immunosorbent assays) for **β-amyloid (Aβ)** and **tau proteins.**
  2) **Blood-based biomarkers**; ***Researchers*** found many plasma proteins, that may contributed in Alzheimer's disease diagnosis (*still researching, and may to be important in the future*).
- **Brain imaging**;
  1) **Computed tomography** (**CT**) and 2) **Magnetic resonance imaging** (**MRI**);
     - Determine volume of brain structures, especially the size of the hippocampus and related regions.
  3) **Single-photon emission computed tomography** (**SPECT**);
     - Small amounts of gamma-emitting radioisotope (radionuclide) are injected, and they are scanned by using a gamma camera.
  4) **Positron emission tomography** (**PET**);
     - Small amounts of radioactive materials called "**radiotracers**" are injected, and they are scanned by using a gamma camera.
     - PET scanning helps in understanding the disease's pathogenesis, making the correct early diagnosis, and monitoring the disease's progression and response to treatment.
     - After IV injection of **radiotracers**, it accumulates in beta amyloid plaques in the patient's brain, which thus become visible via PET.
     - ***Radiotracers for Alzheimer's disease*** (**Amyloid Imaging Agent**);
       1) *In 2012*, the US FDA approved **Florbetapir** ($^{18}$F; fluorine-18 derivative) injection (Amyvid®) by Eli Lilly and Company; is the ***first*** molecular imaging tracer for use in patients being evaluated for possible Alzheimer's disease or other causes of cognitive decline.
       2) *In 2013*, the FDA approved **Flutemetamol** ($^{18}$F) injection (Vizamyl®) is the ***second*** agent used with PET to evaluate Alzheimer's disease and dementia.
       3) *In 2014*, the FDA approved **Florbetaben** ($^{18}$F) injection (Neuraceq®); the ***third*** agent approved.

PET imaging with radiotracers



## ➢ Managements:-

- There is ***no cure*** for AD (treatments offer relatively ***small*** symptomatic **benefit**).
- *The goals of treatment are*;
    - ***Slow*** the **progression** of the **disease** (although this is difficult to do).
    - ***Manage*** **symptoms**, such as behaviour problems, confusion and sleep problems.
    - ***Change*** **home environment**, can better perform daily activities.
    - ***Support*** **family members** and ***other*** **caregivers**.

## Medications

- **Five medications** are **used** to treat the **cognitive problems** of AD;
    - **Tacrine**, **Rivastigmine**, **Galantamine** and **Donepezil** are **acetylcholinesterase inhibitors**.
    - **Memantine** is an NMDA receptor antagonist.
- ***No medication*** has been ***clearly*** **shown** to ***delay*** or ***halt*** the **progression of the disease**.

## I) Cholinesterase Inhibitors

| **Tacrine** | **Donepezil** (Aricept®) |
|---|---|
| **Rivastigmine** (Exelon®) | **Galantamine** (Reminyl®) |

- The ***inhibition*** of **acetylcholinesterase (AChE)** ***within*** the **CNS** will ***improve*** **cholinergic transmission**, at least at those neurons that are still functioning.
- **Tacrine** [TAK-reen] was the ***first*** to ***become*** **available**, but it has been ***replaced*** by others because of its **hepatotoxicity**.
- **Donepezil** [doe-NE-peh-zil], **Galantamine** [ga-LAN-ta-meen] and **Rivastigmine** [ri-va-STIG-meen] are ***reversible*** **AChE inhibitors** ***approved for*** the **treatment of mild to moderate Alzheimer's disease**.
- **All of them** have ***some*** **selectivity** for **AChE** in the **CNS**, as ***compared to*** the **periphery**.
- ***Only*** **Donepezil** is ***approved for*** **treatment of advanced Alzheimer's disease**.
- **Rivastigmine** is the ***only*** **AChE inhibitor** ***available*** as a **transdermal** ***formulation*** and the **only agent** ***approved for*** the **management of dementia associated with Parkinson's disease**.
- **All of them** ***except*** **Rivastigmine** are substrates for **CYP450** and have a potential drug interactions.
- ***Doses***;
    - **Donepezil**;
        - For ***mild*** **to** ***moderate*** **AD**; 5-10 mg once daily.
        - For ***moderate*** **to** ***severe*** **AD**; 10 or 23 mg once daily.
    - **Rivastigmine**;
        - **Tablets**; 1.5 mg orally twice daily, with a maximum dose of 12 mg/day.
        - **Transdermal patches**;
            - **Initial**; **4.6 mg/24 hours**, dose increased slowly (minimum 4 weeks) to **9.5 mg/24 hours** (***maximum effective*** dose of **13.3 mg/24 hours**).
            - * The **transdermal patch 13.3 mg/24 h** is ***approved*** for **all stages** of AD, ***including severe***.
    - **Galantamine**;
        - **Immediate-release** ***formulation***; 4 mg twice daily (initial).
        - **Extended-release** ***formulation***; 8 mg once daily (initial).
        - ***Maintenance dose*** after dose titration is 16-24 mg/day.
- ***Side effects***; **nausea, diarrhea, vomiting, anorexia, tremors, bradycardia** & **muscle cramps**.

# II) N-Methyl-D-Aspartate Antagonists

### Memantine (Ebixa®)

- ***Overstimulation*** of **glutamate receptors,** ***particularly*** of the **NMDA type,** may ***result*** in **excitotoxic effects** on **neurons** and is ***suggested as*** a **mechanism** ***for*** **neurodegenerative** or **apoptotic** (programmed cell death) **processes** via **$Ca^{2+}$** ***release*** **mechanism.**
- **Memantine** [meh-MAN-teen] is an **NMDA receptor** ***antagonist first used*** as an **anti-influenza** ***agent***, it indicated for **moderate to severe Alzheimer's disease** and in **dementia with Lewy bodies.**
- It acts by ***blocking*** the **NMDA receptor** and ***limiting*** **$Ca^{2+}$ influx** into the **neuron.**
- ***Dose***;
  - Immediate-release; 5 mg once daily, and it can be titrated to a maximum dose of 20 mg/day.
  - Extended-release; 7 mg once daily, and it can be titrated to a maximum dose of 28 mg/day.
- ***Common side effects***; **Confusion, dizziness, drowsiness, headache, insomnia** and **agitation.**

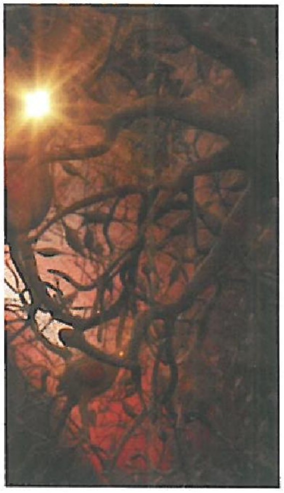
# Nutritional Supplement

### Caprylidene (Axona®)

- **Axona** is a **medical food** used as a dietary management of the impairment of metabolic processes associated with **mild to moderate Alzheimer's disease.**
- It contain fractionated coconut oil (caprylic triglyceride), a medium-chain triglyceride.
- **Axona** has ***not*** been **approved** by the **US FDA** for **Alzheimer's disease.**
- **Axona efficacy** is ***not clear*** and the **Alzheimer's Association** ***doesn't*** **recommend** the **use** of **medical foods,** *including Axona*, for the **treatment of Alzheimer's disease.**
- ***Notes***;
  - ***Some people*** **believe** certain **vitamins** and **herbs** ***may help*** **prevent** or **slowdown AD.**
  - There is ***no strong*** **evidence** that **folate**, **vitamin $B_6$**, **vitamin $B_{12}$**, and **vitamin E** ***prevent*** **AD** or *slows* the **disease.**
  - ***High-quality*** **studies** have ***not shown*** that **ginkgo biloba** ***lowers*** the **chance** of **developing dementia.**

# Focused Ultrasound Therapy

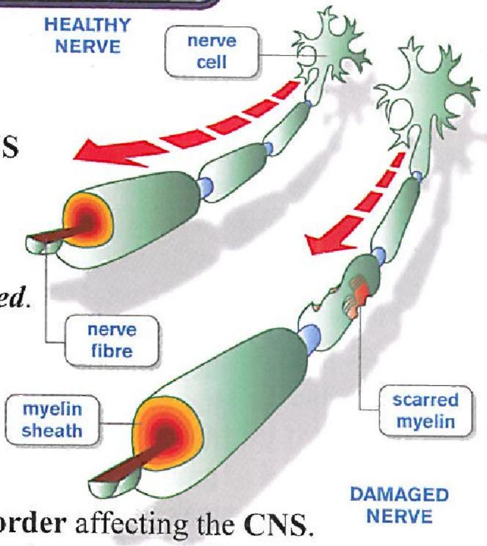
- ***In 2015***, a **pre-clinical study** ***published*** in ***Science Translational Medicine*** **suggests** that **focused ultrasound** may hold a **key** to **providing** a ***non-invasive, non-pharmaceutical*** approach to **treating Alzheimer's disease.**
- ***Study Abstract Summary***;



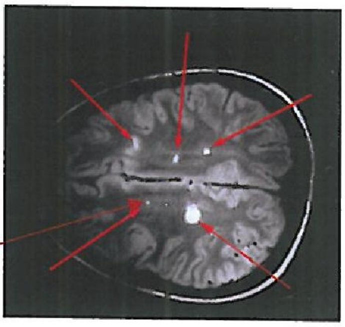
- Is a technique as using a particular type of ultrasound called a focused therapeutic ultrasound, which non-invasively beams sound waves into the brain tissue.
- By oscillating super-fast, these sound waves are able to gently open up the blood-brain barrier (BBB) & stimulate the brain's microglial cells to activate.
- Microglila cells are basically waste-removal cells, so they're able to clear out the toxic beta-amyloid clumps that are responsible for the worst symptoms of Alzheimer's.
- The researchers report fully restoring the memory function of 75% of the mice they tested it on, with zero damage to the surrounding brain tissue.
- The researchers say they are planning on starting trials with higher animal models, such as sheep, and hope to get their human trials underway in 2017.

# Multiple Sclerosis (MS)

➢ **Overview:-**

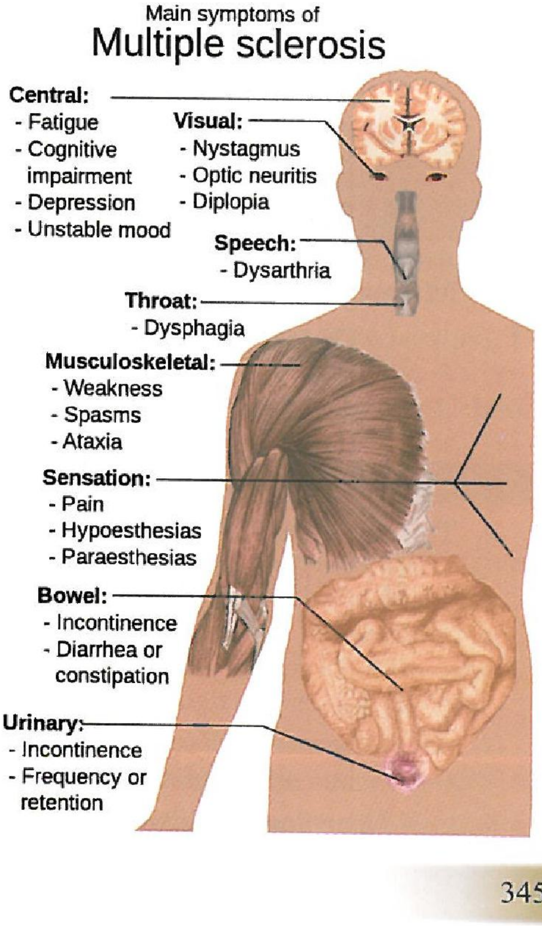

HEALTHY NERVE
nerve cell
nerve fibre
myelin sheath
scarred myelin
DAMAGED NERVE

- **Multiple Sclerosis** (**MS**); is an ***autoimmune disorder***, the **immune system *attacks* myelinated axons** (***destroy* myelin** and **nerve axon**) in the **CNS** (brain and spinal cord).
- **MS** is an ***inflammatory***, ***demyelinating disease*** in which the **insulating covers** (**myelin sheath**) of **nerve cells** in the **brain & spinal cord** are ***damaged***.
- **Signs** and **symptoms** of **MS *vary widely*** and ***depend on*** the **amount** of **nerve damage**.
- **Between attacks, symptoms** may ***disappear*** completely.
- ***Prevalence***;
  - **MS** is the ***most common*** **autoimmune disorder** affecting the **CNS**.
  - **Worldwide**, ***approximately*** **2.1 million** people are affected by **MS**.
  - **MS** is ***usually*** begins ***between*** **20** and **50 years** of **age** and is **twice** as ***common*** in **women** as in **men**.
  - **Whites** and *people of* **northern European *heritage*** are *more likely to* develop **MS**.
  - ***In 2013***, **20,000 people *died*** **worldwide** *from* **MS**, up *from* **12,000 *in 1990***.
- **MS** was ***first described*** in **1868**, and the ***name*** **multiple sclerosis *refers*** to the **numerous scars** (plaques) that ***develop on*** the **white matter** of the **brain & spinal cord**.



➢ **Signs and Symptoms:-**

- *A person with* **MS** can have ***almost any*** **neurological symptom** or **sign**, with **autonomic**, **visual**, **motor**, and **sensory problems**.
- ***Main symptoms*** of **MS**;
  - ***Sensory symptoms***; **Sensory loss** (*early symptoms*) and **pain**.
  - ***Spinal cord symptoms***;
    - Motor; **Muscle cramping**.
    - Autonomic; **Bladder**, **bowel** and **sexual dysfunction**.
  - ***Cerebellar symptoms***; **Charcot triad** of **dysarthria** (cardinal speech symptom), **ataxia** and **tremor**.
  - ***Eye symptoms***; **Optic neuritis**, **diplopia** and **nystagmus**.
  - ***Trigeminal neuralgia***; **Bilateral facial weakness** or **trigeminal neuralgia**.
  - ***Others***;
    - **Facial myokymia**.
    - **Heat intolerance**.
    - **Fatigue** and **dizziness**
  - ***Cognitive difficulties***; ***Difficulty*** to **attention**, **concentration** and **memory**.
  - ***Mood symptoms***;
    - **Depression**; *common*.
    - **Euphoria**; *less common*.
    - **Bipolar disorder**; *May found*.


Main symptoms of
Multiple sclerosis
Central:
- Fatigue
- Cognitive impairment
- Depression
- Unstable mood
Visual:
- Nystagmus
- Optic neuritis
- Diplopia
Speech:
- Dysarthria
Throat:
- Dysphagia
Musculoskeletal:
- Weakness
- Spasms
- Ataxia
Sensation:
- Pain
- Hypoesthesias
- Paraesthesias
Bowel:
- Incontinence
- Diarrhea or constipation
Urinary:
- Incontinence
- Frequency or retention

## Fingolimod (Gilenya®)

- **Fingolimod** [fin-GOL-i-mod] is the ***first oral disease-modifying drug approved by*** the FDA in 2010 to ***reduce*** **relapses** and ***delay*** **disability progression** in ***patients with*** **relapsing forms** of MS.
- ***Mechanism of action***; **Fingolimod** is a **sphingosine-1-phosphate receptor *modulator*, *prevents* activation of T cells.**
- It is ***derived from*** **Myriocin**, a metabolite of the fungus *Isaria sinclairii*, the **treatment cost** is ***very expensive*** (GILENYA® 0.5mg 28 cap.; 15,807 Egyptian pound).
- ***Dose***; 0.5 mg once a day.

**Side Effects**

- **Bradycardia**; ECG monitoring is recommended within 6 months for patients using antiarrhythmics (*including* β-blockers and calcium channel blockers).
- **First**- and **second-degree atrioventricular block.**
- **Hypertension**; Blood pressure monitoring during treatment.
- **Lymphocytopenia**; Risk of infections, particular herpes virus infection, complete blood cell count should be available before therapy starts, discontinue therapy for serious infections.
- **Macular edema** (edema in the macula of the retina); Ophthalmologic examination is needed before and 3-4 months after drug therapy, a history of uveitis or diabetes mellitus increases risk.
- **Respiratory effects**; Decreases in forced expiratory volume (FEV) over 1 second and diffusion lung capacity for carbon monoxide.
- **Liver effects**; Elevations of liver enzymes.
- ***N.B.***; Extended effects of drug for up to 2 months after discontinuation necessitate extended monitoring for many adverse effects.

**Contra indication**

- ***Patients with*** **myocardial infarction, unstable angina, stroke, transient ischemic attack (TIA), decompensated heart failure** or **second**- or **third-degree atrioventricular block.**
- ***Pregnancy***; ***Avoid*** **pregnancy (Category C)** ***during*** **treatment** and for **2 months *after* treatment.**
- ***Avoid*** **live attenuated vaccines** (vaccines less effective during and 2 months after drug treatment).

## Teriflunomide (Aubagio®)

- **Teriflunomide** [TER-i-FLOO-noe-mide] is the active metabolite of **Leflunomide**.
- **Leflunomide** (Arava®) is an **immunosuppressive, disease-modifying antirheumatic drug (DMARD)** ***used in*** **rheumatoid arthritis**; see page no. 486.
- **Teriflunomide** was ***approved by*** the **FDA** in **2012** for the ***treatment of patients with*** **relapsing forms of** MS, the **treatment cost** is ***very expensive*** (price *higher than* GILENYA®).
- ***Mechanism of action***; It is an **oral *immunomodulatory agent*** that ***inhibits*** **pyrimidine synthesis**, The **exact mechanism** in **MS** is ***unknown***, it *may due to*; **antiproliferative** and **anti-inflammatory *effects*** and it *may* ***reduce*** the **number of activated lymphocytes**.
- ***Half life***; ***Long*** **half-life** (8-19 days); ***about*** 3 months to reach steady-state concentrations; ***about*** 8 months to eliminate drug and may take up to 2 years.
- ***Dose***; 7 mg or 14 mg once daily.
- ***Most common side effects***; **Hepatotoxicity**, **Teratogenic *effect***, **GI *effects*** (**diarrhea** and **nausea**), **dermatologic *effects*** (**alopecia** and **rash**), **Hypertension**, **Neutropenia** and **lymphopenia** (***risk of infection, particularly*** **TB infections**).
- ***If women*** **planning** to be **pregnant**, she ***must be*** **discontinue the drug** and ***insure*** the **plasma concentrations** of **Teriflunomide** less than 0.02 mg/L.
- ***FDA black box warning***; ***risk of*** **hepatotoxicity** and **teratogenicity** (***pregnancy*** category X).

## **Natalizumab** (Tysabri®)

- **Natalizumab** [NA-ta-LIZ-ue-mab] is a ***humanized*** **monoclonal antibody** ***against*** the **α-4 subunit of integrin molecules,** ***used*** in the **treatment of multiple sclerosis** and **Crohn's disease**.
- ***Mechanism of action in MS***; ***prevent*** **T-lymphocytes** ***pass*** through the **blood-brain barrier**.
- ***Indication in MS*** as a ***monotherapy*** for the treatment of **patients with relapsing forms of MS**.
- ***Dose in MS***; **300 mg** ***IV infusion*** *over* **1 hour** *every* **4 weeks,** the **treatment cost** is ***very expensive*** (price *higher than* previous drugs).
- ***Side effects/Precautions***;
  - **Progressive Multifocal Leukoencephalopathy**; **PML** (viral CNS infection, John Cunningham virus; JCV); rapidly progressive and usually results in death or permanent disability. The ***risk of PML***; **1**) history of previous immunosuppression. **2**) Long duration of **Natalizumab** treatment, beyond 2 years. **3**) JC virus antibody positivity.
  - ***Common side effects***; **hypersensitivity reactions** (low risk of anaphylaxis), **fatigue**, **headache** and **nausea**.
  - **Antibodies formation** to **Natalizumab** (9-10%), *associated with* ***increased*** **relapses** and **hypersensitivity reactions**.

## **Mitoxantrone** (Novantrone®)

- **Mitoxantrone** [mye-TOX-an-trone] is an ***antineoplastic agent***, it is used in the ***treatment*** of **certain types of cancer**, and it also used to ***treat*** **multiple sclerosis**.
- ***Mechanism of action in MS***; ***decrease*** **monocytes** and **macrophages**, ***inhibit*** **T** and **B cells**.
- ***Indication in MS***; In ***secondary*** **progressive** or **relapsing-remitting MS**.
- ***Dose in MS***; 12 mg/m$^2$ IV infusion every 3 months (maximum lifetime dose: 140 mg/m$^2$).
- ***Because*** of the ***potential for*** **toxicity**, **Mitoxantrone** is ***used only*** patients with ***advancing*** MS who's ***other therapies*** have **failed**.
- ***Toxicity***; **Cardiotoxicity** (risk for heart failure, ECG monitoring must be performed) and **leukemia**.
- ***Pregnancy***; ***Avoid*** **pregnancy (Category D)**.
- ***Precautions***; **laboratory tests** (CBC, bilirubin, liver enzymes, alkaline phosphatase and pregnancy test) ***must be*** **performed** ***before*** **each infusion**.

## **Alemtuzumab** (Lemtrada®)

- **Alemtuzumab** [AL-em-TOOZ-ue-mab] is a ***recombinant*** **monoclonal antibody** ***against*** **lymphocyte antigen** (CD52), it is used in the ***treatment*** of certain types of **lymphocytic leukemia**.
- ***In 2014***, **FDA approved** **Alemtuzumab** (Lemtrada®) for the ***treatment of*** **relapsing forms of MS**.
- ***Mechanism of action in MS***; ***depletes*** **T** and **B cells**.
- ***Indication in MS***; ***Patients with*** **relapsing forms** of **MS**, ***generally*** who have had an ***inadequate*** **response** to **2** or **more** ***other*** **medications**.
- ***Dose in MS***; it is administered as ***2 separate*** **courses** (the **treatment cost** is ***very expensive***, approximately $95,000 for a full course in Germany);
  - **First treatment course**: 12 mg/day IV infusion on 5 consecutive days (60 mg total dose).
  - **Second treatment course**: 12 mg/day IV infusion on 3 consecutive days (36 mg total dose) given 12 months after the first treatment course.
- **Risk Evaluation Mitigation Strategy (REMS) program**; the drug ***must be*** **registered** in a **REMS monitoring program,** ***because of*** the **risk of autoimmunity** (serious, sometimes fatal; such as immune thrombocytopenia), **infusion reactions** (such as anaphylaxis) and **malignancies** (increased risk of malignancies, including thyroid cancer and melanoma).

# II) Symptomatic Therapies

## Fatigue

- **Fatigue** is *one* of the ***most common*** symptom of MS, occurring in ***approximately*** 76-92% of cases.
- There are ***no*** **FDA-approved drugs** for *treatment* of **MS-related fatigue.**
- *Non-pharmacological treatment*; **rest, assistive devices, cooling strategies, exercise, stress management.**
- *Pharmacological treatment*; **Amantadine** (Symmetrel®), **Methylphenidate** (Ritalin®) and **Fluoxetine** (Prozac®).

## Pain

- **Pain** at *some time* of **illness**, is **common** occurrence in patients with MS, ***about*** 30-50% of cases.
- **Pain** in MS ***may be*** **primary** or **secondary**.
- **Primary pain** is ***related to*** the **demyelinating process** and is often ***characterized as*** having a **burning, gnawing** or **shooting quality**;
  - **Tricyclic antidepressants**; are ***first-line drugs*** for **primary pain.**
  - **Anticonvulsants**; *such as* **Carbamazepine**, **Phenytoin** and **Gabapentin** can be added as ***second-line agents***.
- **Secondary pain** in MS is primarily musculoskeletal in nature;
  - **Non-steroidal anti-inflammatory drugs** (**NSAIDs**) or **other analgesics** can be used in secondary pain.

## Spasticity (Muscle tone caused by brain or spinal problems)

- *First line*; **Baclofen** (Lioresal®) and **Tizanidine** (Sirdalud®); *skeletal muscle relaxant agents.*
- *Second line*; **Dantrolene** (Dantrium®), is a direct skeletal muscle relaxant, **Diazepam** (Valium®).
- *Third line*; ***Intrathecal*** **Baclofen.**
- *Focal spasticity*; **Botulinum toxin** (Botox®).

## Walking Impairment

### Dalfampridine (Ampyra®)

- **Dalfampridine** [dal-FAM-pri-DEEN] or **4-Amino-pyridine** is a ***potassium channel blocker.***
- It is the ***only*** **medication** ***approved by*** the **FDA** in 2010 for ***improvement of*** **walking** in **patients** with **multiple sclerosis.**
- *Mechanism of action in MS*; ***prolongs action*** **potentials** in **demyelinated neurons.**
- *Dose*; 10 mg orally twice daily.
- *Most common side effects*; **seizures**, **urinary tract infections** and **insomnia**.
- *Warnings/Precautions*; **Anaphylaxis, Seizures** (dose-dependent) and **urinary tract infection.**
- **Dalfampridine** completed Phase II clinical trials for **Parkinson's disease** in July 2014.

## Pseudobulbar Affect (PBA); Emotional Mismatch

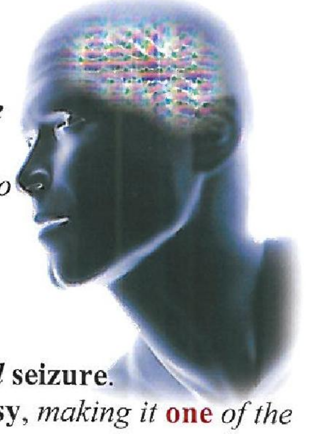
- **Pseudobulbar affect** (PBA) is a **neurological disorder** *characterized by* ***involuntary*** **crying** or **uncontrollable episodes** of **crying** and/or **laughing**, or other **emotional displays.**
- **PBA** occurs ***secondary*** to a **neurologic disease** such as **MS** or **brain injury**.
- *Recent studies* suggest that approximately **10%** of patients with **MS** will experience at least one episode of emotional lability.

### Dextromethorphan/Quinidine (Nuedexta®)

- **Dextromethorphan**; is a cough suppressant drug, **Quinidine**; is an antiarrhythmic drug.
- *Mechanism of action in PBA*;
  - **Dextromethorphan** ***prevents*** **excitatory neurotransmitter release.**
  - *Low-dose* **Quinidine** ***blocks*** **first-pass metabolism** of **Dextromethorphan**, thus ***increasing*** **Dextromethorphan serum concentrations.**
- Nuedexta® contain **20 mg Dextromethorphan Hydrobromide** and **10 mg Quinidine Sulfate.**
- **Nabiximols** (Sativex®); is a ***synthetic*** **cannabinoid mouth spray** used for **neuropathic pain, spasticity, overactive bladder** and ***other*** **symptoms** of **multiple sclerosis** (*not approved by US FDA, but approved in UK and other countries*).

# Epilepsy

## Overview:-



- Epilepsy; is a ***chronic neurological disorder affects*** **people** ***of*** **all ages** ***characterized by*** an ***enduring*** **predisposition** to ***generate*** **epileptic seizures.**
- **Epileptic seizures**; is a ***brief*** **episode** of **signs** or **symptoms** *due to* ***disturbances*** of **electrical activity** in the **brain.**
- **Signs or symptoms**; can include **seizures** or ***periods of*** **unusual behaviour, sensations** and ***sometimes*** **loss of consciousness.**
- ***Prevalence*** (*R; WHO epilepsy fact sheet, updated in Feb. 2016*);
  - ***About*** 10% of **populations** may have a **single *unprovoked*** **seizure**.
  - ***Approximately*** **50 million** people **worldwide *have*** **epilepsy**, *making it* **one** *of the* **most common *neurological diseases*** **globally**.
  - ***Nearly*** **80%** of the people with **epilepsy** live in **low- & middle-income countries.**
  - ***People with*** **epilepsy *respond to*** **treatment *approximately*** **70%** of the time.

## Classification of Seizures:-

- ***According to*** the **International League Against Epilepsy** (**ILAE**), adopted in 1981, with modifications in 2001 and 2010;
  - *In 1981*, the **international classification** of **epileptic seizures** ***from*** **ILAE**; is **2 major** classes; **1**) **Partial-onset seizures. 2**) **Generalized-onset seizures.**
  - The ***recent changes*** in this classification is use of **focal *rather than*** **partial**.

## A) Focal-Onset Seizures

* Is a seizure, which the **electrical disturbances** is ***focused*** in just **one part** of the **brain** (one hemisphere), ***but*** it **can *change into*** a **generalized seizure**, which affects the **whole brain**.

### 1) Simple Focal Seizures

* ***Affect only*** a **small region** *of the* **brain**.

* **Preserved consciousness.**

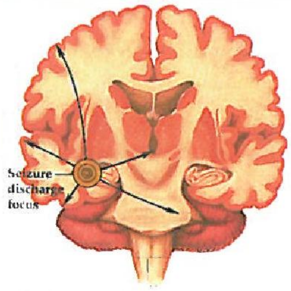
- *Seizures Categories*; **Motor seizures** (change in muscle activity), **Sensory seizures** (changes in any one of the senses), **Autonomic seizures** (changes in automatic functions) and **Psychic seizures** (changes in think or feel).
- ***For example***; The patient may have a sudden onset of clonic jerking of an extremity (*such as* finger or stiffening of part of the body) lasting 60-90 sec., residual weakness may last for 15-30 min. after the attack.

### 2) Complex Focal Seizures

* ***Usually*** **start** in a **small area**, then ***quickly*** involve **other areas** of the brain.

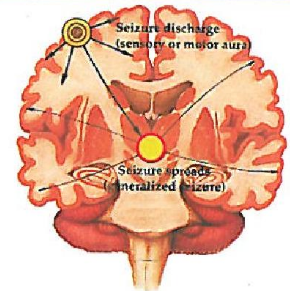
* **Some alteration** or **impairment of consciousness.**

- ***Typically last*** **30 sec.** to **2 min.**, ***but*** may feel tired for several hours after attack.
- An **aura** (warning sign) may **occur** at the *beginning of* a **seizure**, it may consist of a strange smell, taste, sound or visual disturbance, an unexplained feeling of fear or anxiety.
- **Motor behaviour aura** ***called*** **automatisms** (such as finger rubbing, lip smacking, chewing or swallowing or sleepwalking).
- The ***abnormal*** **electrical activity** might ***spread to*** cause a **secondary generalized seizures.**



### 3) Secondarily Generalized Seizures

- ***Often*** **begin** with an **aura** (warning sign) ⇨ ***then into*** a **generalized tonic-clonic convulsion** (see *tonic-clonic convulsion*).
- ***N.B***; The **focal seizures classification** is ***not recommended***, ***i.e.***; ***the terms*** **simple partial seizure, complex partial seizure** and **secondarily generalized seizure** have been ***eliminated from*** **classification**; *however*, they are ***still*** **used** to **describe seizures.**

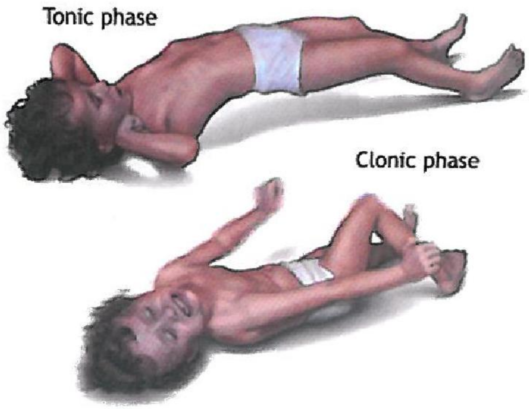


Seizure discharge (sensory or motor aura)
Seizure spreads (generalized seizure)

# B) Generalized-Onset Seizures

* Is a seizure, which the **electrical disturbances** found in the **whole** or a **larger portion** of the brain.
* ***Impair*** in **consciousness**.

## 1) Generalized Tonic-clonic Seizures



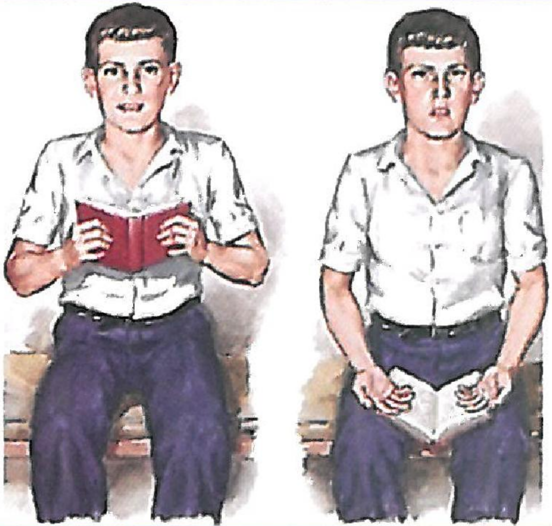
* The ***old term*** is **grand mal** [grahn-mahl] **seizures** (*from the French* **"great illness"**).
* **This type** is what ***most people*** **think** of when they hear the word **"seizure"**.
* ***Typically*** **last 1-3 minutes.**
- A **tonic-clonic seizure** ***comprises*** **two main phases**;

* **Tonic phase** (*comes first and short*); ***Quick*** **loss of consciousness** ⇨ ***falls*** to the **floor** ⇨ ***suddenly*** **muscles tension** (**stiffness**); body flexion and extremities pulled towards the body (***may*** **cry out** *due to* **air** is ***forced from*** the **lungs** and ***may*** **turn blue** in **face**).

* **Clonic phase**; The **arms** and *usually* the **legs** begin to **jerk** ***rapidly*** and **rhythmically** (***rhythmic jerking***) ⇨ after a ***few minutes***, the **jerking** ***slows*** and **stops**.

- **Tongue** *may be* **bitten** and **urinary incontinence** is *common*.
- *Due to* **physical** and **nervous exhaustion**, **sleep** *with* **stertorous breathing** follows an attack.
- ***Before*** the **attack**, a **patient** *may experience* a **prodrome** ***but*** **not** an **aura**.
- The **prodrome** may consist of headache, insomnia, irritability or feeling of impending doom.

## 2) Absence Seizures



* The ***old term*** is **petit mal** [PET-ee-mahl] **seizures** (*from the French* **"little illness"**).
* ***Typically*** begin during **childhood** and ***may persist*** into **adulthood** (***more common*** in **children**).
* ***Short period*** of **impaired consciousness.**
* ***Typically*** **last 10-30 seconds.**
* ***Attack***; *Generally*, ***short period*** of **impaired consciousness** (*may be the* ***only*** **clinical symptom**).
* **Attacks** *may occur* ***up to*** **hundreds** of **times** a **day**.
- ***Diagnosis***; Electroencephalograms (EEGs) performed during seizure activity usually show 3 Hz spike-and-wave complexes.
- **Absence seizures** can be ***further classified as*** typical, atypical, myoclonic absence and eyelid myoclonia.

## 3) Myoclonic Seizures

* **Myoclonic** [MY-o-KLON-ik] **seizures** are a ***brief*** of **sporadic** (isolated) **shock-like jerking** of a **muscle** or ***group*** of **muscles**.
* **Patient** *usually* **awake** and ***able to*** **think** ***clearly***.
* **Jerking movements** ***occurs in*** the **upper** or **lower extremities**, or ***may occur*** in **entire body**.
- They occur in a variety of epilepsy syndromes that have different characteristics

## 4) Atonic Seizures

* **Atonic** [a-TON-ik] **seizures** (*means* "without tone", muscle "tone" is the muscle's normal tension).
* ***Characterized by*** a ***brief loss*** of **muscle tone** and ***falls*** to the **ground** (*also known as* **drop attacks**).
- They begin in childhood and may persist into adulthood.

## 5) Tonic Seizures

* ***Only*** **tonic phase** of a **tonic-clonic seizure**; ***sudden stiffening movements***.

## 6) Clonic Seizures

* ***Only*** **clonic phase** of a **tonic-clonic seizure**; ***rhythmic jerking muscle movements***.

## C) Status Epilepticus (SE)

* **Status Epilepticus** (**SE**) new definition; is ***any seizure*** that **lasts *more than* 5 minutes** or ***more than* one seizure *within*** a **5 minutes** period ***without*** the **person *returning to* normal *between* them.**

- ***Mortality rate***; 10-30%.

## D) Non-epileptic Seizures (NES)

* **Non-epileptic seizures** (NES); are **not *caused by* electrical activity** *in the* **brain.**

- NES can be divided into ***two types***: **organic non-epileptic seizures** and **psychogenic seizures.**

### ➢ Causes:-

- There is ***no identifiable*** **causes** in *about* **half** of **cases.**
- **Epilepsy** ***may occur*** as a **result** of a number of ***other conditions***;
  - **Genetic Factors.**
  - **Infections** e.g. meningitis or viral encephalitis.
  - **Head trauma** e.g. car accidents or other traumatic injury.
  - **Brain tumors** and/or **stroke.**
  - **Lead poisoning.**

### ➢ Triggers of Seizures:-

- ***Many people with epilepsy*** **seizures** can ***occur without*** any obvious **trigger.**
- ***Some people*** will notice **one** or **two triggers** that *may cause* **seizure.**
- **Triggers** can ***differ*** **from person** to **person,** *but* **common triggers** are; **stress, lack of sleep, drinking alcohol, drugs abuse, menstruation cycle** (in women) and **flashing lights.**

### ➢ Life-threatening Complications:-

- **Status Epilepticus** (**SE**); ***risk*** of ***permanent*** **brain damage** and **death.**
- **Sudden Unexplained Death in Epilepsy** (**SUDEP**); ***risk*** of ***sudden unexplained*** **death.**

### ➢ Diagnosis:-

- **Neurological Examination**;
  - Examination of the head, vision, cranial nerves, motor function and sensory function.
- **Laboratory Tests**;
  - Serum glucose, electrolytes, calcium, complete blood cell counts and renal function tests may be necessary.
- **Electroencephalogram** (**EEG**);
  - Used to ***confirm*** the **diagnosis,** ***classify*** **seizures,** ***locate*** the **site of** the **seizures,** and ***select*** the **best seizure medication.**
  - The best time to perform an EEG is while the patient is having seizures. If not possible, it should be performed as soon after the seizure as possible.
- **Brain Imaging**; Computed tomography (CT) and Magnetic resonance imaging (MRI).

### ➢ Managements:-

- **Antiepileptic Drugs**; *Choice of* **drug** *based on*;
  1) **Seizure classification.**
  2) **Frequency and severity of the seizures.**
  3) **Patient-related factors** (age, medical conditions, lifestyle and personal preference).
  4) **Drug-related factors** (cost and drug interactions).
- **Ketogenic Diet**; this is one of the oldest treatments and helps to decrease seizures.
- **Alternative Treatments**; **Biofeedback** (method of using relaxation to change body functions such as breathing, heart rate and blood pressure) **Melatonin** or ***large doses*** of **vitamins.**
- **Epilepsy Surgery**; *by* **1)** ***Remove*** the **area** that ***producing*** **seizures** in the brain or **2)** ***interrupt*** the **nerve pathways** that ***cause*** **seizure** or **3)** ***Implant*** a **device** such as **vagus nerve stimulation.**

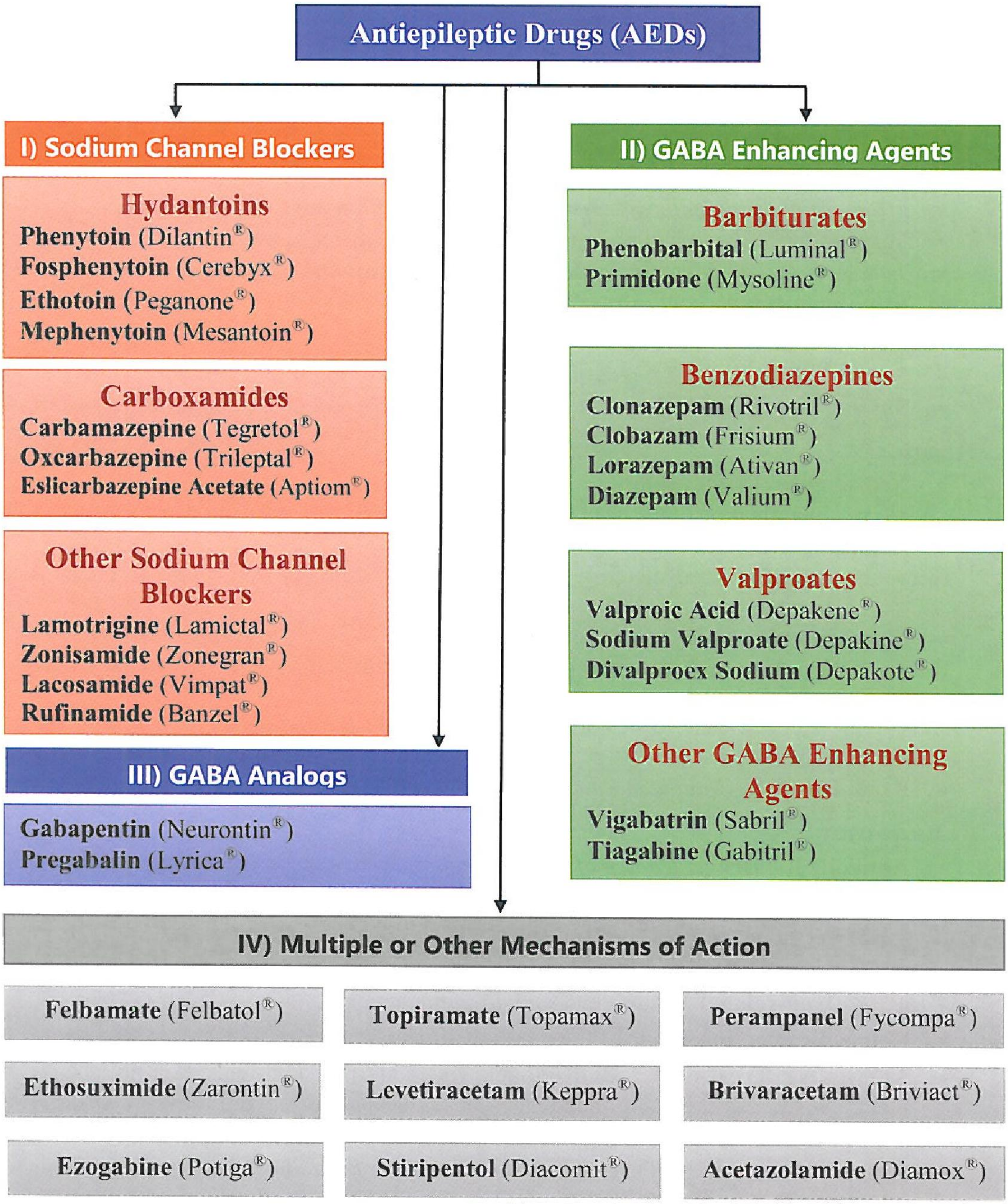
# Antiepileptic Drugs (AEDs)

## General Mechanism of Action of Antiepileptic Drugs:-

- *Blocking* **voltage-gated channels** ($Na^+$ or $Ca^{2+}$).
- *Enhancing* **inhibitory γ-aminobutyric acid** (GABA).
- *Interfering* with **excitatory glutamate transmission.**

- *N.B.*; **Antiepileptic drugs** *suppress* **seizures** ***but*** **do not** "*cure*" or "***prevent***" **epilepsy.**
- **Antiepileptic Drugs** ***Brief History***; In the mid-**1800s**, the first effective anti-seizure medication, **Potassium Bromide**, was introduced. The ***first modern*** treatment, **Phenobarbital**, was developed in **1912**, with **Phenytoin** coming into use in **1938**.

## Antiepileptic Drugs:-



Antiepileptic Drugs (AEDs)

**I) Sodium Channel Blockers**

**Hydantoins**
**Phenytoin** (Dilantin®)
**Fosphenytoin** (Cerebyx®)
**Ethotoin** (Peganone®)
**Mephenytoin** (Mesantoin®)

**Carboxamides**
**Carbamazepine** (Tegretol®)
**Oxcarbazepine** (Trileptal®)
**Eslicarbazepine Acetate** (Aptiom®)

**Other Sodium Channel Blockers**
**Lamotrigine** (Lamictal®)
**Zonisamide** (Zonegran®)
**Lacosamide** (Vimpat®)
**Rufinamide** (Banzel®)

**II) GABA Enhancing Agents**

**Barbiturates**
**Phenobarbital** (Luminal®)
**Primidone** (Mysoline®)

**Benzodiazepines**
**Clonazepam** (Rivotril®)
**Clobazam** (Frisium®)
**Lorazepam** (Ativan®)
**Diazepam** (Valium®)

**Valproates**
**Valproic Acid** (Depakene®)
**Sodium Valproate** (Depakine®)
**Divalproex Sodium** (Depakote®)

**Other GABA Enhancing Agents**
**Vigabatrin** (Sabril®)
**Tiagabine** (Gabitril®)

**III) GABA Analogs**

**Gabapentin** (Neurontin®)
**Pregabalin** (Lyrica®)

**IV) Multiple or Other Mechanisms of Action**

**Felbamate** (Felbatol®)
**Topiramate** (Topamax®)
**Perampanel** (Fycompa®)
**Ethosuximide** (Zarontin®)
**Levetiracetam** (Keppra®)
**Brivaracetam** (Briviact®)
**Ezogabine** (Potiga®)
**Stiripentol** (Diacomit®)
**Acetazolamide** (Diamox®)

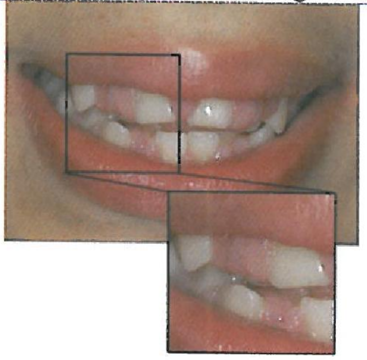
# I) Sodium Channel Blockers

## Hydantoins

### Phenytoin (Dilantin®) (Epanutin®)

- **Phenytoin** [FEN-i-toin] (**PHT**) is the ***oldest non-sedative*** **antiseizure drug.**
- It *was* **known for** decades as **Diphenylhydantoin**.
- ***Mechanism of action***; ***blocks*** **voltage-gated sodium channels** ⇨ ***prolong*** the **inactivation state** of **sodium channels** (**Phenytoin** has ***other*** **effects** on ***several*** **physiologic systems**).
- ***Pharmacokinetics***; **Absorption *depends on* formulations**, *absorption of* **Phenytoin Sodium** *from* the **GIT** is ***nearly*** **complete** and ***highly*** **protein bound**.
  - ***Routes of administration***; **Oral** (capsules or chewable tablets or suspension), **Rectal** and **IV** (IM is not recommended).
  - **Half-life**; *varies from* **12-36 hours**.
  - **Phenytoin** is ***metabolized to*** **inactive metabolites** that are ***excreted in*** the **urine**.
  - * **Phenytoin** is an ***inducer*** of the **CYP3A4** and **CYP2C19** families.
- ***Indications***; **Focal** (or **partial**), **generalized tonic-clonic seizures** and **status epilepticus**.
- ***Dose***; **Orally** 200mg - 500mg daily divided into 1 or 2 doses. **IV *load*.**; 10-15 mg/kg at 25-50 mg/min.

**Side Effects**

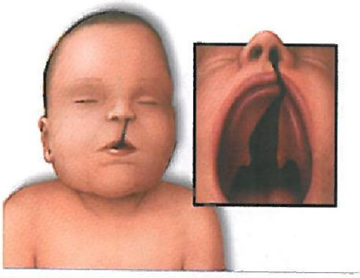


* ***Dose-related side effects***; **Nystagmus**, **Diplopia**, **ataxia** & **drowsiness**.

* ***Non-dose-related side effects*** (***chronic***);

- **Gingival hyperplasia** (gums overgrowth), **hirsutism** ([HUR-soot-iz-um] is a male-pattern hair growth in women), **acne**, **rash**, **hepatotoxicity** and **coarsening of facial features** (change in normal facial features).

- ***Chronic use*** may associated with ***decrease*** **bone mineral density** (*vitamin D metabolism abnormality*) and **megaloblastic anemia**.
- ***IV infusion side effects***; **phlebitis** and **hypotension** (*with rapid infusion*).



- Pregnancy **category D**.

* **Fetal Hydantoin Syndrome**;
  - Cleft lip or palate.
  - Congenital heart disease.
  - Slowing of growth
  - Mental deficiency.

- **Life-threatening fetus bleeding**; decrease vitamin K-dependent clotting factors.

**Drug Interactions**

- ***Drugs that may increase*** **Phenytoin** ***serum levels***;
  - ***Acute*** **Alcohol** abuse, **Warfarin**, **Amiodarone**, ***antiepileptic drugs*** (**Ethosuximide**, **Oxcarbazepine** and **Topiramate**), ***azoles*** (e.g.; **Fluconazole** and **Ketoconazole**), **Capecitabine** (Anticancer drug), **Chloramphenicol**, **Cimetidine**, **Disulfiram**, **Isoniazid**, **Sulfonamides**, **Omeprazole** and **Estrogens**.
- ***Drugs that may decrease*** **Phenytoin** ***serum levels***;
  - ***Chronic*** **Alcohol** abuse, ***anticancer drugs*** (**Bleomycin**, **Carboplatin**, **Cisplatin**, **Doxorubicin**, **Methotrexate**), ***antiepileptic drugs*** (**Carbamazepine**, **Diazepam** and **Vigabatrin**), **Folic acid**, **Diazoxide**, and **Rifampin**.

***Drugs that may either increase or decrease*** **Phenytoin** ***serum levels***;
  - ***Antiepileptic drugs*** (**Phenobarbital**, **Sodium Valproate** & **Valproic acid**).

- ***N.B.***; **Phenytoin** (Healosol® spray) in **wound healing**; **evidence *suggests* that topical phenytoin is *useful* in wound healing** in people with **chronic skin wounds.**

### Fosphenytoin (Cerebyx®)

- **Fosphenytoin** [FOS-phen-i-toin] is a *prodrug* that is ***rapidly converted to*** **Phenytoin** within minutes.

* *Advantages over phenytoin*;

1) **IM dosing** and ***more safely*** **IV dosing.** 2) **Phlebitis** is ***minimized.***
3) **Infusion rate 3 times** *faster* (150 mg/min). 4) ***Can*** **deliver** in **normal saline** or **5% dextrose**.

- *Dose*; 15-20 mg/kg at 100-150 mg/min (1.5 mg of **Fosphenytoin** = 1 mg of **Phenytoin**).
- *Indications*; ***most commonly*** **used in status epilepticus.**
- *Side effects*: **Hypotension**, **perianal itching** and ***other side effects*** of **Phenytoin**.

### Ethotoin (Peganone®)

- **Ethotoin** [ETH-oh-toin] is a ***hydantoin anticonvulsant.***
- *Indications*; ***commonly*** **used in patients** who are ***hypersensitive*** to **Phenytoin**, ***but*** **less effective**.
- *Side effects*; ***less severe*** than **Phenytoin** (***lacks of*** **gingival hyperplasia** and **hirsutism**).

### Mephenytoin (Mesantoin®)

- **Mephenytoin** [meh-FEN-i-toyn] is a ***hydantoin anticonvulsant.*** It is ***metabolized to*** **Nirvanol** (**Ethylphenylhydantoin**), **Nirvanol** is ***quite*** **toxic**. **Mephenytoin** is ***no*** **longer available**.

## Carboxamides

### Carbamazepine (Tegretol®) (Carbatrol®)

- **Carbamazepine** [kar-ba-MAZ-a-peen] (**CBZ**) is a ***major most popular first-line antiepileptic drug for*** **focal seizures** and **generalized tonic-clonic seizures**.
- **Carbamazepine** is ***closely related to*** **Imipramine** and it is a **tricyclic compound** ***effective*** in ***treatment*** **bipolar depression**, the ***value*** in the **treatment** of ***epilepsy*** was ***discovered*** by **chance**.
- *Mechanism of action*; like **Phenytoin**, ***blocks*** **voltage-gated sodium channels**.
- *Pharmacokinetics*; **Absorbed** ***slowly*** after **oral administration** and **varies** ***widely*** **among patients**, ***but complete*** **absorption** apparently ***occurs in*** **all**.

  * **Carbamazepine** is an ***inducer*** of the **CYP1A2**, **CYP2C**, and **CYP3A** families.
- *Formulations*; Tegretol®; **Chewable tablets** 100 mg, 200 mg, **Suspension** 100 mg/5 mL and **Suppositories** 125mg, 250mg. Tegretol® CR or XR; **Extended-release tablets** 100 mg, 200 mg & 400 mg (twice). - *Dose*; 800 mg - 1200 mg divided into 2 or 4 doses.
- *N.B.*; Tegretol® CR or XR, ***must be*** **swallowed whole** and ***never*** **crushed** or **chewed**, while Carbatrol® extended-release capsules ***can be*** **opened** and ***sprinkled on*** **food**.
- *Indications*; **Focal**, **generalized tonic-clonic seizures**, **trigeminal neuralgia** and **bipolar disorder**.

* It is ***not effective*** for **absence seizures** or **myoclonic seizures** (*may increase seizures*).

**Side Effects**

* *Dose-related side effects*;

- **Diplopia**, **ataxia**, **drowsiness** and **mild GI upsets**.
- **Hyponatremia** due to an antidiuretic hormone (ADH)-like effect.

* *Non-dose-related side effects* (*Hematologic side effects*);

* **Aplastic anemia**, **thrombocytopenia** and **leukopenia**.

* *Idiosyncratic side effects*; **skin rash** and **hepatic dysfunction**.

**FDA Warning**

**Hypersensitivity Reactions, HLA-B*1502 and HLA-A*3101 Alleles**

- HLA-B is a human gene that plays a critical role in the immune system.

**A**) Patients with the HLA-B*1502 allele are at a 10-fold elevated risk of Stevens-Johnson syndrome (Type of hypersensitivity reactions);

- Testing is recommended for Asians (including Indians).

**B**) Patients with the HLA-A*3101 allele are also at a 12-fold elevated risk of hypersensitivity syndrome and a 3-fold elevated risk of maculopapular rash;

- No recommendations for testing for this allele have been issued.

**Drug Interactions**

- *Drugs that may increase* **Carbamazepine** *serum levels*; ***CYP3A4 inhibitors***; such as **Cimetidine**, **Diltiazem**, **Verapamil**, **Erythromycin**, **Azoles** & **Isoniazid**.
- *Drugs that may decrease* **Carbamazepine** *serum levels*; ***CYP3A4 inducers***; **Phenytoin**, **Phenobarbital**, **Primidone** **Ethosuximide**, **Theophylline** and **Rifampin**.

## **Oxcarbazepine** (Trileptal®) (Oxtellar® XR)

- **Oxcarbazepine** [ox-kar-BAY-zeh-peen] (**OXC**) is a ***prodrug*** that is ***rapidly reduced*** to the **active monohydroxy** (**MHD**) **metabolite derivatives** (***R*-licarbazepine** and ***S*-licarbazepine**).
- ***Mechanism of action***; like **Phenytoin** and **Carbamazepine** ***blocks*** **voltage-gated sodium channels**.
- **Oxcarbazepine** is ***closely related to*** **Carbamazepine** and is ***useful*** in the **same seizure types**, ***but*** it may have an ***improved*** **toxicity profile**, with ***less potency*** than **Carbamazepine**.
- ***Formulations***;
    - Trileptal®; tablets 150 mg, 300 mg, 600 mg and suspension 60 mg/ml.
    - Oxtellar® XR; extended-release tablets 150 mg, 300 mg, 600 mg.
- ***Dose***; 600 mg - 2400 mg daily divided into 2 or 3 doses.
- ***Indications***; ***Approved*** as ***monotherapy*** or ***adjunctive therapy*** in ***patients with*** **partial seizures**.
- ***Off-label***; **Bipolar disorder**, **diabetic neuropathy** and **trigeminal neuralgia**.
- **Oxcarbazepine** and **MHD** are **CYP3A4 & CYP3A5** ***inducers***, (***less potent than*** **Carbamazepine**).
- ***Side effects***;
    - * **Hyponatremia** ***more common than*** with **Carbamazepine** (***increased with*** **dose** and **age**).
    - **Hematologic** ***side effects less common than*** with **Carbamazepine**.
    - **Hypersensitivity** ***less common than*** with **Carbamazepine** (25-30% of patients with hypersensitivity to **Carbamazepine** will have hypersensitivity to **Oxcarbazepine**).
- ***Drug interactions***; **CYP3A4 *inhibitors or inducers***.

## **Eslicarbazepine Acetate** (Aptiom®)

- **Eslicarbazepine** [es-li-kar-BAZ-a-peen] (**ESL**) **Acetate** is a ***prodrug*** that is ***converted to*** the **active metabolite** **Eslicarbazepine** (***S*-licarbazepine**). ***S*-licarbazepine** is the ***active metabolite*** of **Oxcarbazepine**.
- ***Indications***; **Eslicarbazepine** is ***similar to*** **Oxcarbazepine**. The ***possible advantage*** of **Eslicarbazepine** is ***linear pharmacokinetics*** and ***dose*** is **once daily**.
- ***Formulations***; Aptiom®; tablets 200 mg, 400 mg, 600 mg, 800 mg.
- ***Side effects***; **Dizziness**, **somnolence**, **nausea**, **headache** and **diplopia** (**Hypersensitivity** and **hyponatremia** are ***less common***).

# Other Sodium Channel Blockers

## **Lamotrigine** (Lamictal®)

- **Lamotrigine** [la-MOE-tri-jeen] (**LTG**) is a ***triazine derivate*** that ***inhibits*** **voltage-gated sodium channels**. It was developed as an antifolate agent on the basis of a theory that the mechanism of some AEDs (e.g., **Phenytoin**) is related to their antifolate property.
- ***Mechanism of action***; ***Major mechanism*** is ***blocking*** **voltage-gated sodium channels**, it has been found to ***inhibit*** **glutamate release** and ***inhibits*** **voltage-gated $Ca^{2+}$ channels**.
- It is ***metabolized predominantly*** by **glucuronic acid** ***conjugation***.
- ***Formulations***;
    - Lamictal® tablets; 25 mg, 100 mg, 150 mg, 200 mg.
    - Lamictal® XR; 25 mg, 50 mg, 100 mg, 200 mg, 250 mg, 300 mg.
    - Lamictal® Chewable/dispersible tablets; 2 mg, 5 mg, 25 mg.
    - Lamictal® Disintegrating tablets; 25 mg, 50 mg, 100 mg, 200 mg.
- ***Indications***; ***Monotherapy*** or ***adjunctive therapy*** in **partial**, **generalized**, **absence**, **myoclonic seizures**, **Lennox-Gastaut syndrome** ***associated seizures*** and **bipolar disorder**.
- ***Off-label***; **Peripheral neuropathy**, **trigeminal neuralgia**, **cluster headaches**, **migraines** and ***many*** **psychiatric disorders**.

* ***Side effects*** (***FDA warning***); ***Risk of*** **skin rash** (**Stevens-Johnson syndrome** and **toxic epidermal necrolysis**), which may be ***life-threatening*** **reaction**.

* ***N.B.***; * **Estrogen** (in ***oral contraceptives***) ***increase*** **Lamotrigine clearance**, so ***twice*** the **amount** of **Lamotrigine** ***may be*** **necessary**.

* **Valproic acid** ***decreases*** **Lamotrigine metabolism** and ***dose adjustment*** is **required**.

### Zonisamide (Zonegran®)

- **Zonisamide** [zoe-NIS-a-mide] (**ZNS**) is a ***sulfonamide anticonvulsant*** with ***weak*** **carbonic anhydrase inhibitor** ***effect.***
- *Mechanism of action*; ***Major mechanism*** is ***blocking*** **voltage-gated sodium channels**, it has been found to ***inhibits*** **T-type voltage-gated $Ca^{2+}$ channels.**
- *Indications*; *Approved by* **US FDA** *for* used as ***adjunctive therapy*** in ***patients with*** **focal seizures.**
- *Dose*; 100 mg - 600 mg/d in adults and 4 mg to 12 mg/d in children.
- *Side effects*; **Drowsiness, cognitive impairment** and **skin rashes** (*sulfa allergies*).

* ***N.B.***; ***Concomitant use*** of **Zonisamide** and ***other*** **carbonic anhydrase inhibitors** such as **Topiramate** and **Acetazolamide**, ***increase*** the potential for **metabolic acidosis.**

### Lacosamide (Vimpat®)

- **Lacosamide** [la-KOE-sa-mide] is an ***amino acid derivative.***
- *Mechanism of action*; ***Enhances the*** **slow inactivation** ***of*** **voltage-gated sodium channels.**
- *Indications*; *Approved* as ***monotherapy*** and as ***adjunctive therapy*** for **adolescents 17 years** and **older** with **partial-onset seizures.**
- *Side effects*; **Dizziness, ataxia, vomiting** and **diplopia.**
- *Warning*; **Suicidal ideation, arrhythmia** and **hypersensitivity reactions.**

### Rufinamide (Banzel®)

- **Rufinamide** [roo-FIN-a-mide] is a ***triazole derivative***, with ***anticonvulsant activity.***
- *Mechanism of action*; ***blocking*** **voltage-gated sodium channels** (***not fully*** **understood**).
- *Pharmacokinetics*; **Absorption** ***increased by*** **food.**
- *Indications*; It was ***approved by*** the **US FDA** in **2008** as ***adjunctive treatment*** of ***seizures associated*** with **Lennox-Gastaut syndrome.**
- *Side effects*; **Somnolence, vomiting, fatigue, diarrhea** and **QT interval *shortening*.**

## II) GABA Enhancing Agents

## Barbiturates

### Phenobarbital (Luminal®)

- **Phenobarbital** is (**PHB**) the ***most commonly*** prescribed **antiepleptic drug** in the **20th century**. It is a ***very*** **potent anticonvulsant.** *Currently*, its **use** is ***limited*** *because* of its **adverse effects.**
- *Mechanism of action*; **Phenobarbital** ***potentiate*** the **action** of **GABA** ⇨ ***increase*** **opening** of **$Cl^-$ channels** and ***enhanced*** **hyperpolarization** ⇨ ***Anticonvulsant sedative effects.***
- **Phenobarbital** is a ***powerful*** **inducer** of the **hepatic microsomal enzymes** (**Enzyme Inducing Antiepileptic Drugs; EIAEDs** ***such as*** **Phenytoin**, **Carbamazepine** and **Phenobarbital.**
- *Indications*; ***Usually in*** **status epilepticus** (*emergency*), ***when*** **other agents** ***fail.***

### Primidone (Mysoline®)

- **Primidone** [PRIM-i-done] (**Desoxyphenobarbital**) is ***metabolized*** to **Phenobarbital** (*major*) and **Phenylethylmalonamide**, ***all three compounds*** are **active anticonvulsants.**
- *Mechanism of action*; **Primidone** itself may be ***more like*** that of **Phenytoin.**
- *Indications*; **Partial** and **generalized tonic-clonic seizures,**
- *History*; **Primidone** was once a ***primary*** **anticonvulsant** in the treatment of **partial** and **generalized seizures** and was the ***treatment of choice***, *especially* when ***combined with*** **Phenytoin**, ***but*** in early **1980s**, **Carbamazepine** had ***surpassed*** **Primidone** ***popularity.***

## Benzodiazepines (BDZs)

### **Clonazepam** (Rivotril®)

### **Clobazam** (Frisium®)

### **Lorazepam** (Ativan®)

### **Diazepam** (Valium®)

- *Mechanism of action*; **BDZs** ***potentiate*** the **action** of **GABA** ⇨ ***increase*** **opening** of $Cl^-$ **channels** and ***enhanced*** **hyperpolarization** ⇨ ***Anticonvulsant sedative effects.***
- *Most commonly used drugs*; **Clonazepam** (stronger), **Lorazepam** (longer) and **Diazepam** (faster).
- **Clobazam** is ***widely used*** by **specialist epilepsy clinics** *worldwide*.
- **Clonazepam** is ***most*** **popular**.
- *Indications*; *Usually used as* **adjunctive, short-term therapy** (*emergency*), ***because*** **tolerance** ***may*** **develop**. Full text, see page no. 277

## Valproates (VPAs)

### **Valproic Acid** (Depakene®)

### **Sodium Valproate** (Depakine®)

### **Divalproex Sodium** (Depakote®)

- **Valproates** was ***first made*** in **1882** and came into ***medical use*** in **1960s**.
- **Valproic Acid** [val-PRO-ik A-sid] is a ***fatty carboxylic acids.***
- **Divalproex** [dye-val-PRO-ex] **Sodium** is a ***combination*** of **Sodium Valproate** [val-PROE-ate] ***and*** **Valproic Acid** that is ***converted to*** **Valproate** when it reaches the **GIT**, ***All*** of this **forms** are ***equivalent*** in **efficacy**.
- *Mechanism of action*; is ***not fully*** **understood**, ***possible mechanisms***; ***blockade*** of **GABA transaminase** (*enzyme breakdown of GABA*) and ***blockade*** of **sodium channels** and ***action*** at **T-type calcium channels**.
- *Formulations*; **Valproates** are ***available*** in **multiple-salt dosage forms** and ***extended-release*** **formulations** (Depakine® Chrono).
- *Indications*; **Valproates** are ***very effective against*** **absence seizures**, **myoclonic seizures** and **tonic-clonic seizures**. *Dose*; 1000 mg - 2000 mg daily divided into 1 or 2 doses.
- *Other uses*; **Bipolar disorder** and **migraine prophylaxis**.
- *Most common side effects*; **Nausea**, **vomiting** and **drowsiness**.

* *FDA Warning*; **Fatal hepatotoxicity** (liver enzyme monitoring is needed within the first 6 months), **Severe birth defects** (Spina bifida and lower intelligence quotient; IQ), **fatal pancreatitis** and **suicidal ideation**.

- *Drug interactions*; **Phenobarbital**, **Phenytoin**, **Carbamazepine**, **Oxcarbazepine** and **Primidone**.

## Other GABA Enhancing Agents

### **Vigabatrin** (Sabril®)

- **Vigabatrin** [vye-GA-ba-trin] (**VGB**) is an ***irreversible inhibitor*** of ***GABA aminotransferase*** (**GABA-T**), the **enzyme** ***responsible for*** the **degradation** of **GABA**.
- **Vigabatrin** is a ***racemic*** **compound**, and its (*S*)-**enantiomer** is ***pharmacologically active.***
- *Indications*; **Partial seizures** and **infantile spasms** (*rare epileptic disorder in infants*).
- *Dose*; 2000 mg - 3000 mg/d divided into 1-2 doses, **infant**; 50 mg-150 mg/kg/day in 2 divided doses.
- *Side effects*; **drowsiness**, **dizziness**, **blurred vision** and **weight gain**.

* *FDA Warning*; **Vision loss** (*long-term therapy*) from mild to severe in 30% or more of patients.

### **Tiagabine** (Gabitril®)

- **Tiagabine** [ty-AG-a-been] (**TGB**) is a ***derivative*** of the ***GABA reuptake inhibitor*** **Nipecotic acid**.
- *Mechanism of action*; ***Reversible inhibition*** of the **GABA transporter-1 (GAT-1)** ⇨ ***inhibit*** **GABA reuptake** ⇨ ***increase*** level of **GABA**.
- *Indications*; *approved by* US FDA; ***adjunctive treatment*** for **partial seizures** in **ages 12** ***and*** **up**.
- *Off-label*; **Anxiety disorders** and **neuropathic pain**.
- *Side effects*; **Dizziness**, **paresthesia**, **nervousness**, **tremor** and **depressed mood**.

# III) GABA Analogs

## Gabapentin (Neurontin®)

- **Gabapentin** [GA-ba-pen-tin] (**GBP**) is an ***analog*** (***analogue***) ***of* GABA**, it was *developed to* have a **structure** *similar* to that of **GABA**; however, ***in fact***, **little** or **no action** on the **GABA receptor** or ***enhance*** **GABA actions**, it was originally ***approved by*** the U.S. FDA in **1993**, for use as an ***adjunctive treatment*** for **partial seizures** in **adults**.
- **Gabapentin** has ***anticonvulsant***, and ***anxiolytic effects***.
- ***Pharmacokinetics***; **Absorption** is ***nonlinear***, ***not*** **metabolized** and **eliminated unchanged** ***renally*** (dose adjustments in renal dysfunction).
- ***Mechanism of action***; is ***not fully*** **understood**, it ***decrease*** **$Ca^{2+}$ entry**, by ***binding*** and ***inhibiting*** the $\alpha_2\delta$ (alpha-2-delta) ***subunit*** of the **voltage-dependent $Ca^{2+}$ channels** (this mechanism more contributed in analgesic effect in diabetic neuropathy and post-herpetic neuralgia).
- ***Indications***; ***adjunctive treatment*** for **focal-onset seizures** and **postherpetic neuralgia** (neuropathic pain following shingles; herpes zoster virus).
- ***Dose***; 900 mg - 3600 mg daily divided into 3 doses.
- ***Another formulations***;
  - **Gabapentin** (Gralise®) ***extended-release*** **tablets** 300 and 600 mg, ***indicated only*** for **postherpetic neuralgia** ***not*** **epilepsy**.
  - **Gabapentin Enacarbil** (Horizant®) ***extended-release*** **tablets** 300 and 600 mg, is a ***prodrug*** for **Gabapentin** and is ***indicated for*** **postherpetic neuralgia** and **restless legs syndrome**, ***not*** **epilepsy**.
- ***Side effects***; **Dizziness, fatigue, drowsiness, ataxia, nystagmus** and **tremor**.
- ***Drug interactions***; ***Negligible***.

## Pregabalin (Lyrica®)

- **Pregabalin** [pree-GA-ba-lin] is a ***structural analogue of* GABA**, has ***analgesic***, ***anticonvulsant*** and ***anxiolytic effects***, it was ***approved by*** the U.S. FDA in **2004**.
- **Pregabalin** (Lyrica®) is ***one*** of the **top 10 *most seller* drugs** ($3.4 billion in 2015).
- ***Pharmacokinetics***; like **Gabapentin**, ***not*** **metabolized** and **eliminated** ***renally*** (dose adjustments in renal dysfunction).
- ***Mechanism of action***; ***decrease*** **$Ca^{2+}$ entry**, by ***binding*** and ***inhibiting*** the $\alpha_2\delta$ (alpha-2-delta) ***subunit*** of the **voltage-dependent $Ca^{2+}$ channels**.
- ***Indications***; ***adjunctive treatment*** for **focal-onset seizures**, **diabetic peripheral neuropathy**, **postherpetic neuralgia**, **fibromyalgia** and **neuropathic pain** ***associated with*** **spinal cord injury**.
- ***Dose***; 300 mg daily divided into 2-3 doses.
- ***Side effects***; **Drowsiness, blurred vision, weight gain** and **peripheral edema**.
- ***N.B.***; **Pregabalin** is ***classified as*** **Schedule V controlled substance**, ***abrupt discontinuation***, may cause ***withdrawal symptoms***; **insomnia, nausea, headache** and **diarrhea**.

## IV) Multiple or Other Mechanisms of Action

### Felbamate (Felbatol®)

- **Felbamate** [FEL-ba-mate] is a ***potent anticonvulsant, very effective against*** **multiple seizure types.**
- ***Mechanism of action***; It appears to have ***multiple*** **mechanisms of action**; ***blocking*** **NMDA receptors**, ***blocking*** of **calcium channels** and ***potentiating*** **GABA action.**
- ***Indications***; It is reserved for use in **refractory epilepsies** (***particularly*** **Lennox-Gastaut syndrome**) ***because of*** the ***risk of*** **aplastic anemia** and **hepatic failure.**

### Topiramate (Topamax®)

- **Topiramate** [toe-PYRE-a-mate] is a ***fructose derivative***, *was developed as* an **antidiabetic drug**, ***but*** it was found to have ***very potent anticonvulsant effects.***
- ***Pharmacokinetics***; ***Not*** **metabolized** and **eliminated unchanged** ***renally.***
- ***Mechanism of action***; ***Multiple*** **mechanisms of action**; 1) ***block*** **voltage-gated sodium channels**, 2) ***block*** **voltage-gated calcium channels**, 3) **GABA** ***enhancing*** **action**, 4) ***block*** **AMPA/kainate receptors** (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor is a subtype of glutamate receptors) and 5) ***weak*** **carbonic anhydrase** ***inhibitor.***
- ***Indications***; **Partial** and **generalized tonic-clonic seizures**, **Lennox-Gastaut syndrome**, **migraine prophylaxis**, *in 2012*, it was approved in ***combination with*** **Phentermine** for **weight loss.**
- ***Side effects***; **Somnolence, paresthesia, cognitive slowing, confusion, weight loss, renal stones, glaucoma, oligohidrosis** (*decreased sweating*) and **hyperthermia.**

### Perampanel (Fycompa®)

- **Perampanel** [per-AM-pa-nel] is a ***non-competitive antagonist*** of **AMPA receptor** (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, is a subtype of glutamate receptors).
- ***Pharmacokinetics***; ***Long*** **half-life** (*once-daily*),
- ***Indications***; ***In 2012***, **US FDA** ***approved*** **Perampanel** as ***adjunctive treatment*** for **partial-onset seizures** and ***in 2015*** as ***adjunctive treatment*** for **primary generalized tonic-clonic seizures.**
- ***Side effects***; **Dizziness**, ***aggressive behaviour*** (**irritability, aggression, anger, anxiety**), **drowsiness** and **headache.**
- ***Warning***; ***Serious*** or ***possibly*** **life-threatening mental, mood** or **behaviour problems**, **Perampanel** is designated as a **Schedule III controlled** ***substance.***
- ***N.B.***; **Becampanel, Irampanel, Selurampanel, Talampanel, Tezampanel** are ***new agents*** act as **AMPA** ***receptor antagonist*** in ***clinical trials***, may be ***important*** in the **future** to ***control*** **epilepsy** or **other neurological disease.**

### Ethosuximide (Zarontin®)

- **Ethosuximide** [eth-oh-SUX-i-mide] is a ***succinimide anticonvulsant***, it was introduced in 1960s.
- ***Mechanism of action***; ***blocking*** **T-type $Ca^{2+}$ channels receptors.**
- ***Indications***; ***Only*** **effective** in ***treating*** **absence seizures.**
- ***Side effects***; **Gastric distress, nausea** and **vomiting.**

### Levetiracetam (Keppra®)

- **Levetiracetam** [lee-ve-tye-RA-se-tam] is an *S*-enantiomer of **Etiracetam**, it is a **Piracetam** ***analog.***

* ***Pharmacokinetics***; ***Not*** **metabolized** and **eliminated unchanged** ***renally*** (***No*** **drug interactions**).

- ***Mechanism of action***; ***By binds selectively*** to the **synaptic vesicular protein 2A (SV2A).** The function of this protein is not understood but it is likely that **Levetiracetam** ***modifies*** the **synaptic release** of **glutamate** and **GABA** through an action on vesicular function.
- ***Indications***; ***Adjunctive*** for **focal, myoclonic**, and **primary generalized tonic-clonic seizures.**
- ***Off-label***; **Status epilepticus** (*parenteral formulation*).
- ***Side effects***; **Somnolence, asthenia, ataxia** and **dizziness.**

### Brivaracetam (Briviact®)

- **Brivaracetam** [briv-a-RA-se-tam] is a ***selective, high-affinity*** **synaptic vesicle protein 2A ligand** and ***analog*** of **Levetiracetam.** It ***was approved*** in February 19th, 2016 as ***adjunctive treatment*** of **partial-onset seizures.**

## **Ezogabine** or **Retigabine** (Potiga®)

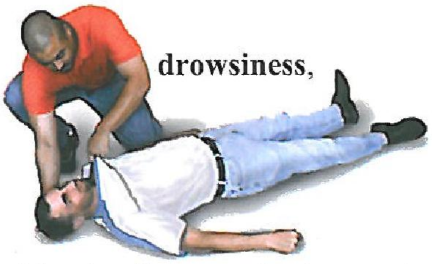
- **Ezogabine** [e-ZOG-a-been] is a ***unique anticonvulsant*** (*novel mechanism*), it ***was approved*** in 2011.
- *Mechanism of action*; **Potassium channel** *opener*.
- *Indications*; ***Adjunctive*** for **partial-onset seizures.**
- *Off-label*; **Tinnitus.**
- *Dose*; 600 mg - 1200 mg/d divided into 3 doses.
- *Side effects*; **Urinary retention, QT interval** ***prolongation*****, blue skin discoloration** and **retinal abnormalities.**
- *N.B.*; **Ezogabine** is ***classified as*** **Schedule V controlled substance.**

## **Stiripentol** (Diacomit®)

- **Stiripentol** [sty-re-PEN-tol] is an ***aromatic allylic alcohol*** in chemical structure.
- *Mechanism of action*; is ***not fully*** **understood**, ***but*** it has been shown to ***enhance*** **GABAergic transmission** in the **brain.**
- *Indications*; ***With*** **Clobazam** and **Valproate** in the ***adjunctive therapy*** of ***refractory*** **generalized tonic-clonic seizures** in **patients** ***with*** **severe myoclonic epilepsy** of **infancy** (**SMEI**, **Dravet's syndrome**). *Dose*; 50mg/kg/day divided into 2-3 doses.
- *Side effects*; **Nausea, vomiting, aggression** and **ataxia** ***due to*** **Stiripentol** (***potent inhibitor*** of CYP3A4, CYP1A2 and CYP2C19) ***increase*** **concentrations** of **Clobazam** and **Valproate.**

## **Acetazolamide** (Diamox®)

- **Acetazolamide** [a-set-a-ZOLE-a-mide] is a ***carbonic anhydrase inhibitor*** (diuretic).
- *Mechanism of action*; ***Mild*** **acidosis** in the brain ***may be*** the **mechanism** by which the drug exerts its **antiseizure activity.**
- *Indications*; ***Effective*** for **all types** of **seizures** ***but*** is ***severely limited*** by the **rapid development** of **tolerance**, with ***return of*** **seizures** usually ***within*** a **few weeks.**
- *Dose*; 250 mg - 1000 mg daily divided into 2 or 3 doses.
- *Side effects*; **Hypersensitivity, nausea, vomiting, paraesthesia, drowsiness, depression** and ***decreased*** **libido.**



### ➢ Status Epilepticus:-

- **General Treatment Principles**;
  - **ABCs**; airway, breathing and circulation.
  - **Laboratory testing**; blood glucose, complete blood cell count, basic metabolic panel, calcium, magnesium, and seizure medicine serum concentrations.
  - ***Give*** an **emergent medication** (*see below*); to **stop** the seizure immediately.
  - ***Follow*** with an **urgent medication** (*see below*) to **prevent** the ***recurrence***.
  - ***In general***, all drugs for **status epilepticus** should be given ***parenterally***.
  - **Neuromuscular-blocking drugs** ***do not*** **stop seizures**; they stop only the muscular response to the brain's electrical activity.
- **Emergency Medications**;
  - **Lorazepam** (Ativan®); ***drug of choice***, ***rapid onset*** (2-3 minutes), ***dose*** 0.1 mg/kg (up to 4 mg/dose) at rate of up to 2 mg/minute; may repeat every 5-10 minutes.
  - **Diazepam** (Valium®); ***rapid onset***, ***short duration***, ***dose*** 0.15 mg/kg (up to 10 mg/dose) at rate of up to 5 mg/minute, may repeat every 5 minutes, **rectal gel** formulation can be given in ***absence*** of **intravenous access.**
  - **Midazolam** (Dormicum®); ***preferred*** for **IM**, **intranasal** or **buccally**, ***rapid onset***, ***short duration***, ***dose*** 0.2 mg/kg (up to 10 mg/dose).
- **Urgent Medications**;
  - **Phenytoin** (Dilantin®); ***dose***, 20 mg/kg less than 50 mg/minute.
  - **Fosphenytoin** (Cerebyx®); ***dose***, 20 mg/kg less than 150/minute.
  - **Phenobarbital** (Luminal®); ***dose***, 20 mg/kg at 50–100 mg/minute.
  - **Valproic Acid** (Depakene®); ***dose***, 20–40 mg/kg at up to 6 mg/kg/minute (*off-label*).
  - **Levetiracetam** (Keppra®); ***dose***, 20-30 mg/kg over 15 minutes (*off-label*).
  - **Lacosamide** (Vimpat®); 200- to 400-mg bolus over 15 minutes (*off-label*).

## ➢ Medication Selection for Various Seizure Types:-

| Drug | Focal | Gen. Tonic-Clonic | Absence | Atypical Absence | Atonic | Myoclonic | Infantile Spasms | Status Epilepticus | Lennox-Gastaut Syndrome |
|---|---|---|---|---|---|---|---|---|---|
| **Na Ch. Blocker** | | | | | | | | | |
| Phenytoin | 🟦 | 🟦 | – | – | – | 🟨 | – | 🟩 | – |
| Carbamazepine | 🟩 | 🟩 | – | – | 🟪 | 🟪 | – | – | – |
| Oxcarbazepine | 🟩 | 🟩 | – | – | 🟨 | 🟨 | – | – | – |
| Eslicarbazepine | 🟪 | – | – | – | – | – | – | – | – |
| Lamotrigine | 🟩 | 🟩 | 🟦 | 🟪 | 🟨 | 🟨 | – | – | 🟩 |
| Zonisamide | 🟩 | 🟨 | 🟨 | – | – | 🟪 | – | – | – |
| Lacosamide | 🟩 | – | – | – | – | – | – | 🟨 | – |
| Rufinamide | 🟪 | 🟨 | 🟨 | – | 🟨 | – | – | – | 🟩 |
| **GABA Enhancing** | | | | | | | | | |
| Phenobarbital | 🟦 | 🟦 | 🟦 | – | – | 🟨 | – | 🟦 | – |
| Primidone | 🟦 | 🟦 | 🟦 | – | – | – | – | – | – |
| Clobazam | 🟪 | 🟪 | 🟨 | – | – | 🟨 | – | – | 🟩 |
| Clonazepam | 🟨 | 🟨 | 🟦 | 🟦 | 🟩 | 🟦 | 🟦 | – | 🟩 |
| Lorazepam | 🟨 | 🟨 | 🟨 | 🟨 | – | 🟨 | – | 🟩 | – |
| Diazepam | – | – | – | 🟪 | – | 🟪 | 🟪 | 🟩 | 🟦 |
| Valproic Acid | 🟦 | 🟩 | 🟩 | 🟩 | 🟩 | 🟩 | 🟩 | 🟦 | – |
| Vigabatrin | 🟥 | 🟥 | – | – | – | – | 🟥 | – | – |
| Tiagabine | 🟪 | – | – | – | 🟪 | 🟪 | – | – | – |
| **GABA Analogs** | | | | | | | | | |
| Gabapentin | 🟩 | 🟦 | – | – | – | – | – | – | – |
| Pregabalin | 🟪 | – | – | – | – | – | – | – | – |
| **Multiple or Others** | | | | | | | | | |
| Felbamate | 🟥 | 🟥 | 🟥 | – | – | 🟥 | – | – | 🟥 |
| Topiramate | 🟩 | 🟩 | 🟨 | – | 🟨 | 🟩 | – | – | – |
| Perampanel | 🟪 | – | – | – | – | – | – | – | – |
| Ethosuximide | – | – | 🟩 | 🟩 | – | 🟪 | – | – | – |
| Levetiracetam | 🟩 | 🟩 | 🟪 | – | – | 🟨 | – | 🟨 | – |
| Ezogabine | 🟪 | – | – | – | – | – | – | – | – |
| Acetazolamide | 🟪 | 🟪 | 🟨 | 🟨 | – | – | – | – | – |

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| | | | |
|---|---|---|---|
| 🟩 | First-line drug | 🟪 | Adjunctive treatment |
| 🟦 | Second-line drug | 🟥 | Only when benefits outweigh risks |
| 🟨 | May be used | | |

*Table from American College of Clinical Pharmacy (ACCP) Updates in Therapeutics 2015*

- **Newly diagnosed epilepsy**; First line drug ⇨ If seizures persist ⇨ Second line drug ⇨ If seizures persist ⇨ Adjunctive therapy ⇨ If seizures persist ⇨ Vagal nerve stimulation.

## ➢ Selected Interactions between Antiepileptic Drugs:-

**Drug Interactions**

| | Initial (First) Drug | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Add-on (Second) Drug** | **Carbamazepine** | **Clobazam** | **Eslicarbazepine** | **Ezogabine** | **Felbamate** | **Lamotrigine** | **Oxcarbazepine** | **Perampanel** | **Phenobarbital** | **Phenytoin** | **Primidone** | **Rufinamide** | **Topiramate** | **Valproic acid** | **Zonisamide** |
| **Carbamazepine** | | | 🟪 | 🟪 | 🟪 | 🟪 | 🟪 | 🟪 | | 🟪 | 🟥 | 🟪 | 🟪 | 🟪 | 🟪 |
| **Eslicarbazepine** | | 🟥 | | | | | | | | 🟥 | | | | | |
| **Ethosuximide** | 🟪 | | | | | | | | | | | | | | |
| **Felbamate** | 🟪 | | | | | | | | | | | | | 🟥 | |
| **Lamotrigine** | | | | | | | | | | | | | 🟪 | | |
| **Oxcarbazepine** | | | | | | | | 🟪 | 🟥 | 🟥 Or No | | | | 🟪 | |
| **Perampanel** | | | | | | | | | | | | | | | |
| **Phenobarbital** | 🟪 | | 🟪 | | | 🟪 | 🟪 | | | 🟪🟥 | | 🟪 | | 🟪 | 🟪 |
| **Phenytoin** | 🟪 | | 🟪 | 🟪 | 🟪 | 🟪 | 🟪 | 🟪 | 🟥 | | 🟥 | 🟪 | 🟪 | 🟪 | 🟪 |
| **Primidone** | 🟪 | | | | | 🟪 | | | | | | 🟪 | | 🟪 | |
| **Rufinamide** | 🟪 | | | | | 🟪 | | | 🟥 | 🟥 | | | | | |
| **Topiramate** | | | | | | | | | | 🟥 | | | | 🟪 | |
| **Valproic acid** | | | | | | 🟥 | 🟪 | | 🟥 | 🟪 | | 🟥 | 🟪 | | |
| **Vigabatrin** | | | | | | | | | | 🟪 | | | | | |

- ***Colour Guide***;

| | |
|---|---|
| 🟪 | - The **add-on drug** ***decrease*** serum concentration of the **initial drug**. |
| 🟥 | - The **add-on drug** ***increase*** serum concentration of the **initial drug**. |
| 🟪🟥 | - The **add-on drug** ***increase*** or ***decrease*** serum concentration of the **initial drug**. |

- ***Example***; If the Felbamate ***added to*** Carbamazepine therapy, it will ***decrease*** the serum concentration of Carbamazepine, but if added to Valproic acid therapy, it will ***increase*** the serum concentration of Valproic acid.

- *N.B.*; This interactions ***not means*** the drugs are **not added**, ***but means*** **added** ***with*** **precautions** and ***after*** the **dose adjustment**.

*Table from American College of Clinical Pharmacy (ACCP) Updates in Therapeutics 2015*

- **Special Populations:-**

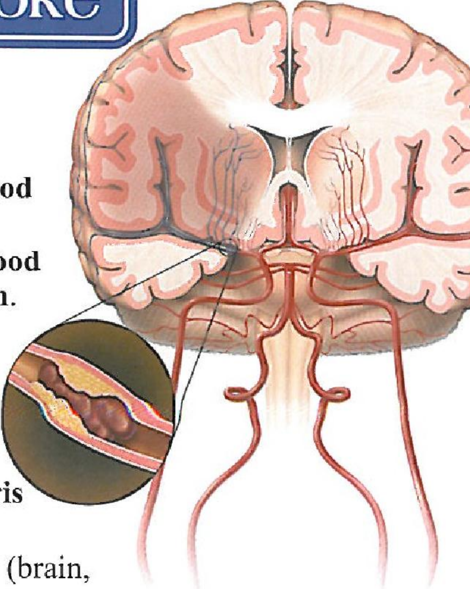
## Older Adults

- ***Drugs that may be affected***;
  - **Carbamazepine**; decreased clearance.
  - **Phenytoin**; decreased protein binding if hypoalbuminemia or renal failure.
  - **Valproic acid**; decreased protein binding.
  - **Diazepam**; increased half-life.
  - **Primidone**; decreased clearance if creatinine clearance (CrCl) is low.
  - **Lamotrigine**; decreased clearance.
- Antiepileptics ***with*** **renal elimination** ***must be*** **adjusted** according to the CrCl value.

## Women's Health

- ***During marriage life***, women with epilepsy should;
  - Take the best drug for their seizure type.
  - Treated with monotherapy, if possible.
  - **Carbamazepine**, **Clobazam**, **Eslicarbazepine**, **Felbamate**, **Lamotrigine**, **Oxcarbazepine**, **Perampanel**, **Phenobarbital**, **Phenytoin**, **Primidone**, **Rufinamide** and **Topiramate** are ***decrease*** the **hormonal contraceptive** (oral, patch, vaginal ring and implant) ***effectiveness***.
  - Use **Folic acid** supplementation with no less than 0.4 mg/day.
- ***Epilepsy during pregnancy***;
  - ***Avoid use of***; **Phenytoin**, **Carbamazepine** and **Phenobarbital**, *if possible.*
  - ***Avoid use of***; **Valproic acid** and **Lamotrigine** ***during*** the **first trimester**, *if possible.*
  - ***Avoid use of***; **antiepileptic drug combination.**
  - ***Drug monitoring*** needed if used; **Lamotrigine**, **Carbamazepine**, **Phenytoin**, **Levetiracetam** and **Oxcarbazepine**.

# Ischemic Stroke



## ➢ Overview:-

- **Strokes**; classified into *two* **major categories**;
  - A) **Haemorrhagic strokes**;
    - 1) **Intracerebral haemorrhage (ICH)**; **blood vessel** ***bursts*** **within the brain.**
    - 2) **Subarachnoid haemorrhage (SAH) blood vessel** ***bursts*** on the **surface of the brain.**
  - B) **Ischemic strokes**;
    - 1) **Thrombotic stroke**; **blood clot** ***forms*** in **one of the arteries** that ***supply*** **blood** *to the* **brain.**
    - 2) **Embolic stroke**; **blood clot** or *other* **debris forms** *away from* the **brain.**
- *Loss* of **blood circulation** to an **area** of the **CNS** (brain, spinal cord or retina), ***this leads to*** **poor oxygen** ***supply*** or **CNS infarction** (CNS hypoxia), ***resulting*** **loss** of **neurologic function.**
- *Definitions* (From American Heart Association/American Stroke Association; AHA/ASA 2013);
  - Ischemic Stroke; An ***episode of*** **neurological dysfunction** *caused by* **focal cerebral, spinal** or **retinal** ***infarction*** **(CNS infarction).**
  - CNS Infarction; Is **brain, spinal cord** or **retinal cell** ***death*** *attributable to* **ischemia,** ***based on***; Pathological, imaging, or other objective evidence of cerebral, spinal cord, or retinal focal ischemic injury in a defined vascular distribution; or clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury based on symptoms persisting ≥24 hours or until death, and other etiologies excluded.
- *Ischemic Stroke Prevalence*;
  - **Stroke** is the ***major cause*** of **disability** and the ***fourth major cause*** of **death** in the **United States.**
  - ***Each year***, *approximately* **795,000 people** in the **United States** ***experience*** **new** (610,000 people) or **recurrent** (185,000 people) stroke.
  - ***According to*** the **World Health Organization (WHO), 15 million** people ***suffer*** **stroke worldwide** ***each year***. Of these, **5 million** ***die***, and another **5 million** are ***left permanently*** **disabled.**

## ➢ Signs and Symptoms:-

- *Common* **stroke signs** and **symptoms** *include the following* (range from mild to severe);
  - Difficulty speaking (slurred speech) and understanding problems.
  - Paralysis or numbness of the face, arm or leg, and walking problems.
  - Vision problems in one or both eyes, severe headache, dizziness or vertigo.
- If the **brain** *becomes* **damaged** ***irreversibly*** and **infarction occurs**, the **symptoms** may be permanent, ***stroke warning signs***, **FAST**;

Face
Look for an uneven smile
Arm
Check if one arm is weak
Speech
Listen for slurred speech
Time
Call emergency at the first sign

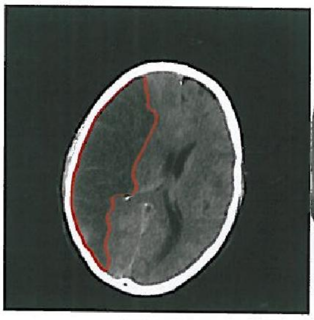
## ➢ Risk Factors:-

- ***Non-modifiable*** **risk factors;**
    - **Age**; Risk doubles each decade (10 years) after 55 years.
    - **Race**; African-Americans have a higher risk of stroke than other races (*except Native Americans*).
    - **Sex**; Risks are greater for men than for women; however, women more likely to die of strokes than are men.
    - **Family history**; Protein C and S deficiencies or factor V Leiden mutations.
- ***Modifiable*** **risk factors** *(American Heart Association/American Stroke Association; AHA/ASA guideline 2013)*;

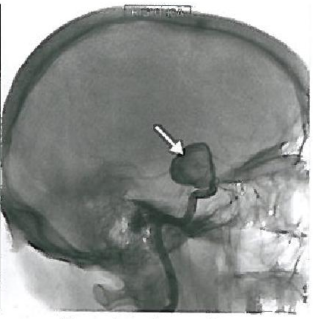
| Risk Factor | Risk *vs* Normal | Risk Reduction After Modify |
|---|---|---|
| Smoking | 1.9 times | 50% |
| Hypertension | 1.4-8 times | 32% |
| Atrial Fibrillation | 2.6-4.5 times | 68% (*with warfarin*) |
| Coronary Heart Disease | 1.55 times (♀) - 1.73 times (♂) | |
| Asymptomatic carotid stenosis | 2 times | 50% (*with endarterectomy*) |
| Peripheral Artery Disease | 3 times | unknown |
| Dyslipidemia | 1.5-2 times | 27-32% (*with statins*) |
| Diabetes mellitus | 1.8-6 times | unknown |
| Physical Inactivity | 2.7 times | unknown |
| Obesity | 1.75-2.37 times | unknown |
| Pregnancy | 2.4 times | |
| Sickle Cell Disease | 200-400 times | 91% (*with transfusion therapy*) |
| Oral Contraceptives | <50 mcg of estrogen; double risk<br>>50 mcg of estrogen; 4.5 times | |
| Postmenopausal Hormone Therapy | 1.4 times | |
| Depression | 1.35 times | |

## ➢ Diagnosis:-

- **Physical examination** and **blood tests**; to detect symptoms and causes of stroke.
- **Computerized tomography** (**CT**) and **magnetic resonance imaging** (**MRI**); can show a hemorrhage, tumor, stroke and other conditions.
- **Carotid ultrasound**; can show a build-up of fatty deposits (plaques) and blood flow in the carotid arteries.



CT-scan



Cerebral angiogram

- **Cerebral angiogram**; can show a detailed view of arteries in the brain and neck.

## ➢ Prevention and Managements:-

### Acute Management

### General Measures

- **ABCs**; **airway**, **breathing** and **circulation**.
- *Complete* **initial evaluation** and **assessment**, *including* **imaging** and **laboratory testing**, ***within*** **60 minutes** of **patient arrival**.
- **Hyperglycemia** is ***common*** after ***acute*** **ischemic stroke**, even in **patients *without* diabetes**, use of **IV Insulin** to maintain serum glucose in the range of 72-135 mg/dL in the first 24 hours.
- When **hypoglycemia** is ***discovered***, the glucose level must be adjusted to a normal level. **IV fluids**, such as **Dextrose** 25% or **Dextrose** 50% may be necessary.

# Fibrinolytic Therapy

* The ***only*** **fibrinolytic agent** that has been shown to ***benefit*** in **acute ischemic stroke** is **tissue plasminogen activators** (**t-PAs**).

* **Streptokinase** ***may benefit*** patients with **acute MI**, ***but*** in **acute ischemic stroke** it has been ***shown*** to ***increase*** the **risk** of **intracranial hemorrhage** and **death**.

## Alteplase (Activase$^{R}$)

- **Fibrinolytic therapy**, ***restore*** **cerebral blood flow** *in some patients* with **acute ischemic stroke** and *may* ***lead to*** **improvement** or **resolution** of **neurologic deficits**.
- ***Unfortunately***, **Fibrinolytic therapy** *may* cause ***symptomatic*** **intracranial hemorrhage**.
- The **AHA/ASA** *inclusion* **guidelines** ***for the administration*** of **t-PAs** are as *follows*;
    - **Tissue plasminogen activator** (**tPA**) administered ***within*** **4.5 hours** ***after*** **symptom onset**.
    - ***Dose***; 0.9 mg/kg (not to exceed 90-mg total dose) infused over 60 minutes with 10% of the total dose administered as an initial bolus over 1 minute.
    - **Intracerebral hemorrhage** ***increased but no increase*** in **mortality**.
    - **Exclusion criteria** (***Contraindications***);
        - ***Minor*** or ***rapidly*** **improving stroke signs** or **symptoms**.
        - **Intracranial** or **subarachnoid bleeding** (or **history**).
        - ***Other*** **active internal bleeding**.
        - **Intracranial surgery, head trauma, stroke** ***in past*** **3 months**.
        - **Major surgery** or **serious trauma** ***within*** **2 weeks**.
        - **GIT** or **urinary tract hemorrhage** ***within*** **3 weeks**.
        - **Blood pressure** ***greater than*** 185/110 mm Hg.
        - **Glucose** ***less than*** 50 mg/dL or ***greater than*** 400 mg/dL.
        - **Arterial puncture** at a ***noncompressible site*** or **lumbar puncture** ***within*** **1 week**.
        - **Seizure** ***at stroke onset***.
        - **Intracranial neoplasm**, **arteriovenous malformation** and **aneurysm**.
        - **Active treatment** ***with*** **Warfarin** (INR greater than 1.7), **Heparin** (elevated activated partial thromboplastin time), or **platelet count** ***less than*** 100,000 cells/mm3
        - ***Post***-**myocardial infarction** ***in past*** **3 months**.
        - **Pregnancy**.
- In ***patients*** **not eligible** for **tissue plasminogen activator**; **Aspirin** (160- to 325-mg initial dose with 50- to 100-mg maintenance dose) ***within*** **48 hours** of **stroke onset** is ***recommended***.
- **Ultrasound Therapy**; Researchers have studied the use of **transcranial ultrasound** as a means of ***assisting*** **t-PAs** in ***fibrinolysis***, By delivering mechanical pressure waves to the thrombus, ultrasound can theoretically expose more of the thrombus's surface to the circulating fibrinolytic agent.

# Endovascular Procedures

- ***Another*** **treatment option** is an **endovascular procedure**, *called* "**mechanical thrombectomy**"; ***strongly recommended***, in which a **large blood clot** is ***removed*** by sending a wired-caged device called a **stent retriever**, to the site of the blocked blood vessel in the brain.

# Primary Prevention

## Risk Factors Modification

- ***Modifiable* risk factors** *include the following*;
  - Hypertension
  - Dyslipidemia
  - Postmenopausal HRT
  - Weight and body fat
  - Cigarette smoking
  - Atrial fibrillation
  - Depression
  - Diabetes
  - Sickle cell disease
  - Diet and activity

## Patient Education

- Patients should be educated ***about* stroke warning signs** and instructed to seek emergency care if they experience any of them.

## Vitamin K Antagonists (Old Oral Anticoagulants)

### Warfarin (Coumadin®) (Marevan®)

- It is ***more effective*** than **Clopidogrel *plus* Aspirin**.
- **Intracranial bleeding** is ***more common***, require **INR monitoring** (range 2-3).
- ***Used*** in patient has **atrial fibrillation** and **mitral stenosis** or **prosthetic heart valve**.

## Novel Oral Anticoagulants (NOACs)

- The **AHA/ASA** have released ***updated* guidelines** on the **primary prevention of stroke**, the ***new recommendations*** include ***use*** of **new oral anticoagulants**, *including* **Dabigatran**, **Rivaroxaban** and **Apixaban**, in ***patients with* non-valvular atrial fibrillation**.
- Full text, see page no. 213.

### Dabigatran Etexilate (Pradaxa®)

- ***Mechanism of action***; **Direct thrombin inhibitor.**
- ***Dose***;
  - ***Patients with*** creatinine clearance (CrCl) **>30 mL/min**; **150 mg** taken orally, ***twice daily***.
  - ***Patients with*** severe renal impairment (CrCl **15-30 mL/min**); **75 mg *twice daily***.
- ***Side effects***; **GI bleeding** (low risk of intracranial hemorrhage).
- ***Contraindications***;
  - ***Patients with*** a CrCl **<15 mL/ min.** or ***advanced* liver disease**.
  - ***Patients with* prosthetic heart valve**.
- ***N.B.***; The **capsule *should not*** be **opened** because it ***increases* bioavailability** by **75%**.
- ***Dabigatran antidote***; **Idarucizumab** (Praxbind®) is a monoclonal antibody and the ***first* reversal agent** for the **Dabigatran** has been approved by the FDA in October 16, 2015.

### Rivaroxaban (Xarelto®)

- ***Mechanism of action***; **Direct factor Xa inhibitor.**
- ***Dose***; 20 mg orally once a day.
- ***Side effects***; **GI bleeding** (low risk of intracranial hemorrhage).
- ***Contraindication***; ***Patients with*** a CrCl **<15 mL/ min.**

### Apixaban (Eliquis®)

- ***Mechanism of action***; **Direct factor Xa inhibitor.**
- ***Dose***; 5 mg taken orally twice daily, **dose adjustment** with **CYP3A4 *inhibitors*** or ***inducers***.
- ***Side effects***; **bleeding.**

# Secondary Prevention

## Risk Factors Modification

- ***All* risk factors *must be* modified**;
    - Smoking cessation, cholesterol-lowering medications, blood pressure adjusted at <140/<90 mmHg, carotid revascularization, diet modifications and exercise.

## Antiplatelet Therapy

### Aspirin (Aspocid®)

- *Dose*; **75-100 mg/day** orally.

### Dipyridamole/Aspirin (Aggrenox®)

- Aggrenox®; Contains **Dipyridamole** ***extended-release*** (200 mg) and **Aspirin** (25 mg).
- *Dose*; 1 capsule orally twice daily.
- *Side effects*; **Headache**, **nausea** and **dyspepsia**.

### Clopidogrel (Plavix®)

- *Dose*; **75 mg/day** orally.
- *Metabolism*; **Clopidogrel** is a ***prodrug*** that requires activation via the **cytochrome P450** ***enzyme*** isoform **CYP2C19**, there may be ***interactions*** with **CYP2C19** ***inhibitors*** (**Omeprazole**).
- The ***combination*** of **Clopidogrel** with **Aspirin** for ***long-term*** stroke prevention is ***discouraged***.

### Cilostazol (Pletal®)

- **Cilostazol** is ***extensively metabolized*** in the liver by the CYP3A4, 2C19 and 1A2 isoenzymes.
- *Dose*; 100 mg orally twice daily on an empty stomach.
- *Side effects*; **Headache**, **GI side effects** and **palpitation**.
- *FDA warning*; **Cilostazol** is *contraindicated* in **patients with congestive heart failure**.

## Anticoagulants

### Warfarin (Coumadin®) (Marevan®)

- In ***patient with*** **atrial fibrillation**, **rheumatic mitral valve disease**, **mechanical prosthetic heart valves**, **bioprosthetic heart valves** or **left ventricular mural thrombus formation**.
- **Intracranial bleeding** is ***more common***, require **INR monitoring** (range 2-3).

# Headache

## ➢ Overview:-

- **Headache** (*also known as* **Cephalalgia**); is the ***symptom*** of **pain** ***anywhere*** in the **region** ***of the*** **head** or **neck**.
- ***Frequent*** **headaches** *can affect* **relationships** and **employment**.
- There are a ***number*** of **different classification systems** *for* **headaches**. The ***most*** **recognized** is that of the **International Headache Society** (IHS).
- **Treatment** of a **headache** ***depends on*** the **underlying cause**, ***but commonly involves*** **pain medication**.
- ***About*** **half** of **adults** *have* a **headache** in a **given year**.

The Head ache

An 1819 caricature by George Cruikshank depicting a headache

## ➢ Classification:-

- There are ***more than*** **200 types** of **headaches**. Some are ***harmless*** and some **are life-threatening**.
- **Classification of headache**, ***from*** **second edition** of The **International Classification of Headache Disorders** *by* **International Headache Society** (IHS);

A) **Primary Headaches**; are **benign**, **recurrent** and ***not caused*** by **underlying disease** or **structural problems** (90% of all headaches are primary);

1) **Migraine** (18% of women, 6% of men in US).
2) **Tension-type headache** (88% of women, 69% of men in US).
3) **Cluster headache** (0.2% of the general population).
4) **Other primary headaches**;

| | |
|---|---|
| Primary stabbing headache | Transient and localised stabs of pain in the head that occur spontaneously in the absence of organic disease of underlying structures or of the cranial nerves. |
| Primary cough headache | Headache precipitated by coughing or straining in the absence of any intracranial disorder. |
| Primary exertional headache | Headache precipitated by any form of exercise. |
| Primary headache associated with sexual activity | Headache precipitated by sexual activity. |
| Hypnic headache | Attacks of dull headache that always awaken the patient from asleep. |
| Primary thunderclap headache | High-intensity headache of abrupt onset mimicking that of ruptured cerebral aneurysm. |
| Hemicrania continua | Persistent strictly unilateral headache responsive to indomethacin (responds only to indomethacin). |
| New daily-persistent headache (NDPH) | Headache that is daily and unremitting from very soon after onset (within 3 days at most). |

B) **Secondary Headaches**; are **harmless** or **dangerous** and ***caused by*** an **underlying disease**, like an **infection**, **head injury**, **vascular disorders**, **brain bleed** or **tumors**;

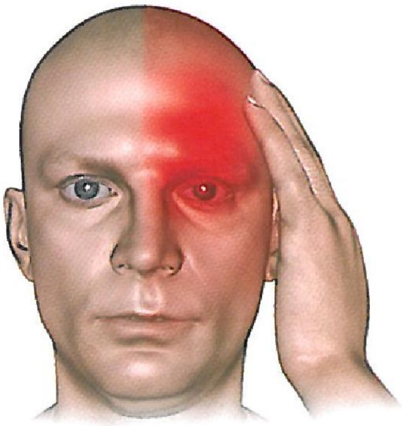
5) Headache attributed to head and/or neck trauma.
6) Headache attributed to cranial or cervical vascular disorder.
7) Headache attributed to non-vascular intracranial disorder.
8) Headache attributed to a substance or its withdrawal.
9) Headache attributed to infection.
10) Headache attributed to disorder of homoeostasis.
11) Headache or facial pain attributed to disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cranial structures.
12) Headache attributed to psychiatric disorder.

C) **Cranial neuralgias**, **facial pain** and **other headaches**;

13) Cranial neuralgias and central causes of facial pain.
14) Other headache, cranial neuralgia, central or primary facial pain.

# Migraine

## ➢ Overview:-



- **Migraine**; is a ***primary*** **headache disorder** ***characterized by*** **recurrent headaches** that are **moderate *to* severe**.
- The **word** ***derives from*** the **Greek** (**hemikrania**), (**hemi**), "**half**", & (**kranion**), "**skull**", "**pain on one side of the head**".
- *Usually* **last** ***from*** **4 *to* 72 hours (3 days).**
- ***Some*** **cases** ***associated with*** **warning signs** (**aura**), *such as* flashes of light, blind spots or tingling in the arm or leg.
- **Migraine** is ***most common*** in **women** and ***has a strong*** **genetic factors**.
- ***Changing*** in **hormone levels** ***may*** also **play a role** in **migraine**.
- *Prevalence*;
  - *Globally*; *approximately* **15%** of **people**. *In US*; **18%** of **women** and **6%** of **men**.
  - *In children*, *about* **1.7%** of **7 year olds** & **3.9%** of **7-15 years**.
  - *Most commonly*; *start*, **15-24 years olds** & occur ***most frequently***, **35-45 years olds**.

## ➢ Migraine Stages (Phases):-

### 1) Prodrome

- Occur in about 60% of patients, **one *or* two days before a migraine**, may ***including***; constipation, irritability, depression or euphoria, food cravings and uncontrollable yawning.

### 2) Aura (Warning Signs)

- ***Before*** or ***during*** **migraine headaches**, ***begins gradually***, commonly ***lasts*** for **20-60 min.**, ***including***; most commonly visual disturbances (scintillating scotoma, shimmering glittering zigzag border), ***but*** can be sensory (needles sensations in arm or leg) or speech problems.

### 3) Pain or Attack

- Usually ***lasts*** from **4-72 hours**, ***including***; from moderate to severe, pain on one side or both sides of the head, pulsating or throbbing, sensitivity to light and sounds, nausea and vomiting.

### 4) Postdrome

- Occurs after a migraine attack, commonly ***lasts*** for some days, ***includes***; cognitive difficulties, GI symptoms, mood changes and weakness.

## ➢ Symptoms and Signs:-

- **Typical symptoms** of **migraine** ***include the following***: (TV-~~ON~~-SD)

| | |
|---|---|
| **Throbbing (Pulsating) Pain** | - Pain with each beat of the heart, with moderate to severe. |
| **Visual Disturbances "Aura"** | - Visual disturbances are considered a common warning sign of classical migraine (migraine with aura; MWA, *see next*). |
| **One Sided Head Pain** | - Most of patients feels; one-sided head pain (unilateral).<br>- *Some* of patient feels; pain on both sides, in their neck, or at the front or back of their head (bilateral). |
| **Nausea or Vomiting** | - Nausea (80%) and vomiting (50%) are very common. |
| **Sensitivity to Light and Sound** | - Sensitivity or aversion to light and sound is one of the most common signs of migraine. |
| **Dizziness** | - Dizziness is common. |

## ➢ Classifications (or Types) and Diagnostic Criteria:-

### 1) Migraine Without Aura (MWOA) or Common Migraine

- It is the commonest subtype of migraine (80% of migraines), and don't occur with aura.
- ***Diagnostic criteria*** (*according to the IHS*);
  - **The 5, 4, 3, 2, 1 criteria**;
    - **Five** or more attacks (*within 4h to 3d*).
    - **Four** hours to **Three** days in duration (untreated or unsuccessfully treated).
    - **Two** or more of the following;
      - Unilateral (one-sided head pain).
      - Pulsating.
      - Moderate or severe pain intensity.
      - Aggravation by or causing avoidance of routine physical activity (e.g.; walking or climbing stairs).
    - **One** or more of the following;
      - Nausea and/or vomiting.
      - Sensitivity to both light (photophobia) and sound (phonophobia).

### 2) Migraine With Aura (MWA) or Classic Migraine

- Less common than migraine without aura (15% migraines), and occur with aura.
- ***Diagnostic criteria*** (*according to the IHS*);
  - At ***least* 2 attacks *with at least* 3** of the **following 4 characteristics**;
    1) One or more fully reversible aura symptom.
    2) At least one aura symptom develops gradually over more than 4 minutes.
    3) No individual aura symptoms last for more than 60 minutes.
    4) Headache follows aura within 60 minutes after the aura ends.

### Uncommon Types of Migraine

3) **Childhood periodic syndromes that are commonly precursors of migraine**; include **cyclical vomiting** (occasional intense periods of vomiting), **abdominal migraine** (abdominal pain, usually accompanied by nausea), and **benign paroxysmal vertigo of childhood** (occasional attacks of vertigo).
4) **Retinal migraine**; involves migraine headaches accompanied by visual disturbances or even temporary blindness in one eye.
5) **Complications of migraine**; migraine headaches and/or auras that are unusually long or unusually frequent, or associated with a seizure or brain lesion.
6) **Probable migraine**; Probable migraine conditions that have some characteristics of migraines, but where there is not enough evidence to diagnose it as a migraine with certainty (in the presence of concurrent medication overuse).

## ➢ Pathophysiology:-

- **Migraines pathophysiology** remain ***incompletely understood.***
- **Migraines** are ***believed to*** be a **neurovascular disorder** with evidence supporting its mechanisms ***starting*** within the **brain** and then ***spreading*** to the **blood vessels.**
- The *common* **theories *that explain* migraines pathophysiology**, *include*;
  - **Vascular Theory**; **Intracranial VC** is ***responsible for*** the **aura**, & subsequent **rebound VD** & **activation** of **perivascular nerves** ***resulted*** are ***responsible for*** **headache.**
  - **Neurovascular Theory**; **Migraine** is ***primarily*** a **neurogenic process** *with secondary* ***changes*** in **cerebral perfusion.**
  - **Cortical Spreading Depression (CSD) Theory**; **wave** of **neuronal excitation** in the **cortical gray matter** that ***spreads*** from its site of origin at the rate of 2-6 mm/min.
  - ***High levels*** of the **serotonin**, are believed to be involved.
  - ***Some evidence*** **supports** a primary role for **brainstem** and **diencephalon.**

## ➢ Causes:-

- The **underlying causes** of migraines are ***unknown.***
- However, they are believed to be ***related to*** a mix of **environmental** and **genetic factors.**

## ➢ Migraine Triggers:-

**Hormonal**

Menstruation
Pregnancy
Menopause

**Lifestyle**

Smoking
Emotional stress
Sleep disturbances
Not eating or skipping meals

**Foods**

Caffeine
Chocolate
Alcohol (Red wine)
Aspartame (sweetener)
Aged cheese (tyramine food)
Monosodium glutamate (MSG)
Ice cream (*ice not cream*)
Smoked fish and meats
Processed meat
Citrus fruits
Onions, Nuts
Avocados, Tomatoes,

**Environmental**

Bright, flash or fluorescent light
Strong odour (perfumes)
Weather changes

**Medications**

Oral contraceptives
Vasodilators

## ➢ Managements:-

### Acute Attack Treatment

| Triptans | | |
|---|---|---|
| **Sumatriptan** (Imitrex®) | **Zolmitriptan** (Zomig®) | **Rizatriptan** (Maxalt®) |
| **Naratriptan** (Amerge®) | **Eletriptan** (Relpax®) | **Almotriptan** (Axert®) |
| **Frovatriptan** (Frova®) | | |

- **Sumatriptan** [SOO-ma-TRIP-tan], **Zolmitriptan** [ZOLE-mi-TRIP-tan], **Rizatriptan** [RYE-za-TRIP-tan], **Naratriptan** [NAR-a-TRIP-tan], **Eletriptan** [EL-e-TRIP-tan], **Almotriptan** [AL-moe-TRIP-tan], and **Frovatriptan** [FROE-va-TRIP-tan] are ***selective*** **agonists** for **5-HT$_{1B}$** and **5-HT$_{1D}$** receptors.
- **Triptans** are a family of tryptamine-based drugs, introduced in the 1990s for the ***treatment*** of **migraines** and **cluster headaches.**
- All of these agents available in oral preparation, **Sumatriptan** available in nasal, SC and rectal preparation, **Zolmitriptan** available in nasal preparation, **Zolmitriptan** and **Rizatriptan** are available in an oral disintegrating tablet.
- There is also a ***combination preparation*** of **triptan/nonsteroidal anti-inflammatory (NSAIDs)**; **Sumatriptan/Naproxen** (Treximet®), ***indicated for*** the ***acute treatment*** of **migraine with** or **without aura**, and more ***effective*** in **menstrual migraine.**

- *Mechanism of action*; **Triptans** are *selective agonists* for **$5\text{-HT}_{1B}$** and **$5\text{-HT}_{1D}$ receptors**;
  1) *Inhibit* **the release of vasodilating peptides** (*especially* **calcitonin gene-related peptide; CGRP**).
  2) **Vasoconstriction** *effect* on **intracranial blood vessels**.
- *Contraindication*; Patients with **coronary artery disease, stroke, uncontrolled hypertension, peripheral vascular disease & pregnancy** (Category C; when benefits outweigh the risks).
- **Serotonin syndrome** may reported during co/administration of **Triptans** with **SSRIs, MAOIs**, or other **antidepressant drugs (TCAs)**.

- *General Principles*;
  - * **One dose** for **early/mild headache**.
  - * *May be* **repeated** *after* **two hours**.
  - * **Do not use** *more than* **two doses** within a **24-hours**.
  - * **Do not use** *more than* **2-3 days** *weekly*.
  - * **NSAIDs, opioids & antiemetics** *may* be **used** *with* **triptans**.
  - * **Ergot alkaloids** *cannot* be **taken** on the **same day** *with* **triptans**.

**Dose**

| Triptans | Dosage Forms | Maximum Daily Dose |
|---|---|---|
| **Sumatriptan** (Imitrex®) | Tablets; 25 mg, 50 mg, 100 mg | 200 |
| | SC injection; 4 mg, 6 mg | 12 |
| | Intranasal; 5 mg, 20 mg | 40 |
| **Zolmitriptan** (Zomig®) | Tablets 2.5 mg, 5 mg | 10 |
| | Disintegrating tab.; 2.5 mg, 5 mg | 10 |
| | Intranasal 2.5 mg, 5 mg | 10 |
| **Rizatriptan** (Maxalt®) | Tablets; 5 mg, 10 mg | 30 |
| | Disintegrating tab.; 5 mg, 10 mg | 30 |
| **Naratriptan** (Amerge®) | Tablets; 1 mg, 2.5 mg | 5 |
| **Eletriptan** (Relpax®) | Tablets; 20 mg, 40 mg | 80 |
| **Almotriptan** (Axert®) | Tablets; 6.25 mg, 12.5 mg | 25 |
| **Frovatriptan** (Frova®) | Tablets; 2.5 mg | 7.5 |
| **Sumatriptan/Naproxen** (Treximet®) | Tablets; 85 mg/500 mg | 170/1000 |

## Ergot Alkaloids

**Ergotamine** (Ergomar®)

**Dihydroergotamine** (D.H.E. 45®) (Migranal®)

- **Ergometrine** [er-go-MET-reen], **Dihydroergotamine** [dye-hye-droe-er-GOT-a-meen] are an **ergots** that used in *acute treatment* of **migraine** (*should be* considered for **patients** with **nausea** or **vomiting**).
- **Ergotamine**, it is often *combined with* **Caffeine** to *facilitate* **absorption** of **ergot alkaloids**.
- **Dihydroergotamine** has *non*-**oral administration routes** (subcutaneous, intravenous and intranasal).
- *Mechanism of action*; it has similar actions to the **triptans**, acting as an *agonist* to the **$5\text{-HT}_{1D}$** *causing* **vasoconstriction** of the **intracranial blood vessels**.
- *Dose*;
  - **Ergotamine** (Ergomar®); **Initial dose**: **2 mg** under the tongue, *may be* **repeated** *after* **30 minute (must** *not exceed* **3 tablets** per day; **6 mg), total weekly dose; 10 mg**.
  - **Dihydroergotamine** (D.H.E. 45®) (Migranal®);
    - *Intranasal*; **1 spray** (0.5 mg) into each nostril (**1 mg**), *may be* **repeated** *after* **15 minutes (must** *not exceed* **2 mg** per day), the total **weekly dose**; 8 sprays (**4 mg**).
    - *IV/IM/SC*; **1 mg** after the *first symptom*, *may be* **repeated** *after* **1 hour (must** *not exceed* **3 mg** per day), the *total* **weekly dose**; **6 mg**.
- *Contraindication*; Patients with **coronary artery disease, stroke, uncontrolled hypertension, peripheral vascular disease & pregnancy** (**Category X**; uterine contractions, fetal distress, gastrointestinal atresia and miscarriage).
- *Drug interactions*; with **potent CYP3A4 inhibitors**, *elevates* the **serum levels** of **Ergotamine**, increase the *risk for* **vasospasm** leading to **cerebral ischemia** and/or **ischemia of the extremities**.

## Analgesics

- Non-Steroidal Anti-Inflammatory; NSAIDs (Simple Analgesics);
  - For *only moderate* migraine attacks *not associated with* vomiting or severe nausea, NSAIDs (*include* Paracetamol) or combination analgesics are *first choice agents* because they are *effective*, *less expensive*, and *less side effects* than triptans or ergots.
  - When *moderate* attacks are *associated with* severe nausea or vomiting, an oral or rectal antiemetic drug can be used in *conjunction with* NSAIDs.
- Opioid Analgesics; Opioids and Barbiturates *should not be used* for the *treatment* of moderate to severe migraine, *except* as a last resort, due to their *potential for* tolerance and dependence.

## Antiemetics

- IV Metoclopramide, and IV or IM Chlorpromazine and Prochlorperazine can be *used as* monotherapy for acute migraine headache, act as antiemetics *mainly* because they are dopamine antagonists. In addition, they are *effective* for *reducing* migraine headache pain.
- Oral antiemetics *should not be considered as* monotherapy in acute migraine, used in *adjunctive therapy* (Metoclopramide) with NSAIDs to *decrease* nausea and vomiting.

## Other Agents

- Isometheptene; is a *sympathomimetic amine* sometimes *used in* combination in the treatment of migraines due to its *vasoconstricting properties*.

## Combinations

- *Common Combination Egyptian Brands*;
  - Paracetamol + Metoclopramide (Migracid®).
  - Ergotamine 1mg + Caffeine 100mg + Metamizole (or Analgin *like NSAIDs*) 300mg (Amigraine®).
  - Ergotamine 1mg + Paracetamol 325mg + Caffeine 100mg + Metoclopramide 5mg (Metograine®).
  - Ergotamine 1mg + Meprobamate (*like Barbiturates*) 150mg + Metamizole 200 mg + Pentobarbital 10 mg + Caffeine 50mg (Migrainil®).
- *Common Combination World Brands*;
  - Acetaminophen 300mg (*Paracetamol name in USA*) + Codeine 15, 30, 60mg (Tylenol® No.3).
  - Acetaminophen 325mg + Isometheptene 65mg + Dichloralphenazone 100mg (Midrin®).
  - Butalbital (*Barbiturates*) 50mg + Aspirin 325mg + Caffeine 40mg (Fiorinal®).
  - Acetaminophen 250mg + Aspirin 250mg + Caffeine 65mg (Excedrin® Migraine).

## Status Migrainosus

- *Status Migrainous*: Attack of migraine, with headache phase *lasting more than* 72 hours *despite treatment*. Headache-free intervals of *less than* 4 hours.
- Patients need to be *hospitalized* for a short period and may need to be treated with *intravenous* Valproate or Dihydroergotamine or Corticosteroids for a few days.

## Migraine Prophylaxis

*** High efficacy
** Low efficacy
* Limited efficacy

A) Antihypertensives; Beta Blockers (Propranolol*** and Timolol***), Calcium Channel Blockers (Verapamil** and Flunarizine***), Centrally Acting Agents (Clonidine**) ACEIs (Lisinopril*), Angiotensin-Receptor Blockers (Candesartan*).

B) Antiepileptics; Valproate***, Topiramate***, Lamotrigine**, Gabapentin* and Oxcarbazepine*.

C) Antidepressants; TCAs (Amitriptyline***, Nortriptyline***, Doxepin*** and Protriptyline***), SSRIs (Paroxetine*, Fluoxetine* and Sertraline*).

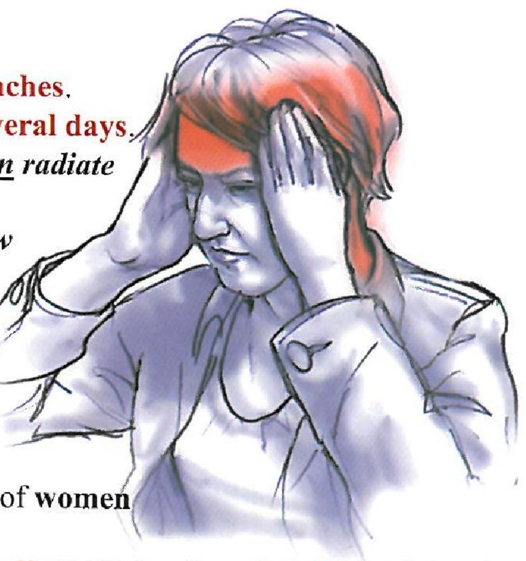
D) Serotonin Antagonists; Methysergide***, Pizotifen*** and Cyproheptadine**.

E) Botulinum Toxin; *Clostridium botulinum* toxin type A *** (Botox®) *Approved*.

F) Melatonin; Melatonin *supplements* may be *useful* in migraine prophylaxis.

G) Devices; TENS (Transcutaneous Electrical Nerve Stimulation) device*** (Cefaly® device), *Approved*.

# Tension-type Headache (TTH)



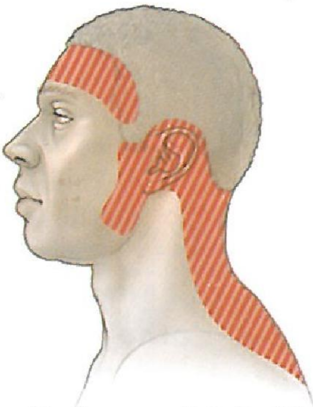
## ➢ Overview:-

- Is the *most common type* of **headache**.
- They are commonly referred to as **stress headaches**.
- These **headaches** may *last from* **30 min**. to **several days**.
- **Pain** is *like* **band squeezing the head**, and *can radiate* to the **lower back of the head**.
- **Attacks** of *mild* to *moderate* headache with *few* **associated symptoms**.
- *Prevalence*;
  - As of **2013** tension headaches affect about **1.6 billion** *people* (**20.8%** of *population*).
  - *In general population* ranging between **30%** and **78%** in *different studies*.
  - In **US** tension headaches affect about **88%** of **women** and **69%** of **men**.
- *Duration*; Tension-type headaches can be **episodic** (**>15 days**) or **chronic** (**<15 days**).
- *Tension-type headaches are divided into*;

## ➢ IHS Tension Headache Subtypes:-

- **Infrequent Episodic**; Headache occurring on <1 day per month (<12 days per year).
- **Frequent Episodic**; Headache occurring on ≥1 but <15 days per month for at least 3 months (≥12 and <180 days per year).
- **Chronic Tension-type Headaches**; Headache occurring on ≥15 days per month on average for >3 months (≥180 days per year).

## ➢ IHS Diagnostic Criteria:-



A) *At least* **10 previous headaches**, each *lasting from* **30 min**. to **7 days**.
B) **Headache** has *at least* **two of the following characteristics**;
  1) **Bilateral location.**
  2) **Pressing/tightening** (*non*-**pulsating**) **quality**.
  3) **Mild** or **moderate intensity**.
  4) *Not* **aggravated** by **routine physical activity** *such as* **walking**.
C) *Both of the following*;
  1) *No* **nausea** or **vomiting** (anorexia may occur).
  2) *No more than* **one** of **photophobia** or **phonophobia**.

## ➢ Pathophysiology; *both* **muscular** and **psychogenic factors** are believed to be associated with tension-type headache.

## ➢ Causes:-

- **Stress**; may cause contraction of neck and scalp muscles (no evidence confirms that the origin of pain is sustained muscle contraction).
- **Anxiety**, **poor posture** and **depression**.

## ➢ Managements:-

### Acute Attack Treatment

A) **Simple Analgesics**; *such as* **Aspirin**, **Ibuprofen**, and **Paracetamol**.

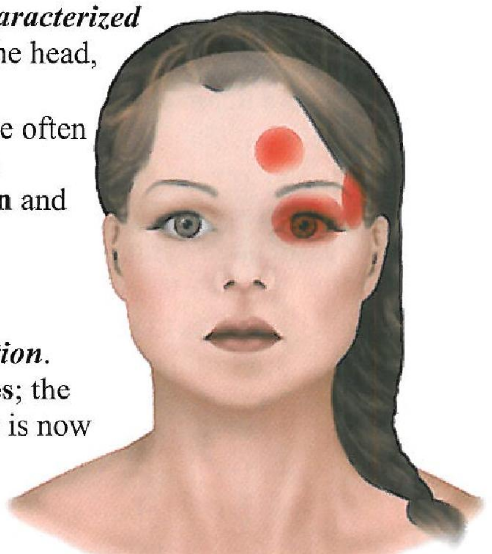
B) **Analgesic/combinations**; are *widely used*.

### Prophylaxis Medications

- **Tricyclic Antidepressants**; **Amitriptyline** and **Nortriptyline** are the most commonly used.
- **Evidence** is *insufficient* for the use of **SSRIs**, **Propranolol** and ***Clostridium botulinum* toxin type A**.

# Cluster Headache (CH)

## ➢ Overview:-

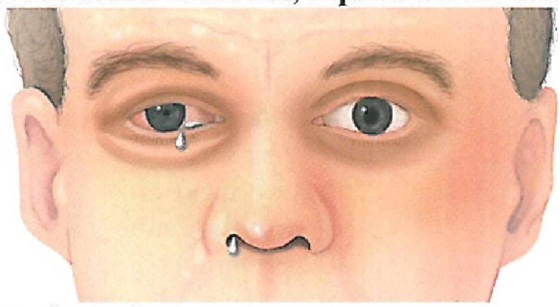


- *Cluster headache*; is a **neurological disorder** ***characterized by*** **recurrent**, **severe headaches** on **one side** of the head, ***typically*** **around *the* eye**.
- ***Also known as*** **histamine headache**, and there are often ***accompanying*** **autonomic symptoms** ***during*** the **headache** such as **eye watering**, **nasal congestion** and ***swelling*** **around the eye**.
- *Prevalence*;
  - CH is ***relatively uncommon***.
  - CH affecs ***about*** **0.2%** of the ***general population***.
  - CH is ***more common*** in **males** ***than*** in **females**; the **male-to-female** ratio was 6:1 in the 1960s but is now closer to **2:1**.

## ➢ IHS Cluster Headache Subtypes:-

- **Episodic Cluster Headache**; Headache attacks occurring in periods lasting 7 days to 1 year separated by pain-free periods lasting 1 month or longer.
- **Chronic Cluster Headache**; Headache attacks occurring for more than 1 year without remission or with remissions lasting less than 1 month.

## ➢ IHS Diagnostic Criteria:-



A) ***At least*** **5 previous headaches**, **severe** or **very severe unilateral orbital**, **supraorbital** and/or **temporal pain** ***lasting*** **15-180 minutes**.

B) ***At least*** **1** of the following ***must occur***;

1) **Conjunctival injection** and/or **lacrimation**.
2) **Nasal congestion** and/or **rhinorrhoea**.
3) **Eyelid oedema**.
4) **Forehead** and **facial sweating**.
5) **Miosis** and/or **ptosis**.
6) **Sense of restlessness or agitation**.

C) **Attacks** have a ***frequency*** from **1 *every* other day** to **8 per day**.

## ➢ Pathophysiology; *Not fully understood*, *but* 3 major aspects of the pathophysiology;

1) Trigeminal distribution of pain. **2**) Circadian rhythmicity. **3**) Autonomic features.

## ➢ Managements:-

### Acute Attack Treatment

A) **Oxygen**; **100%** via ***non-rebreather*** **face mask** at 12 to 15 L per minute for 15 to 20 minutes, ***relieves*** **pain** in **50-85%** of **patients**.

B) **Triptans**; SC and ***intranasal*** **Sumatriptan** and ***intranasal*** **Zolmitriptan** are **effective**. **Oral formulations** usually ***do not act quickly enough***, ***but*** **oral Zolmitriptan** showed ***efficacy*** in **one trial**.

C) **Intranasal Lidocaine**; **20-60 mg** as a **nasal drop** or **spray** (1 mL of 10% solution applied bilaterally with a cotton swab for five minutes).

D) **Octreotide** (**Somatostatin *analogues***; **growth hormone *inhibitor***), 100 mcg SC have been used.

### Prophylaxis Medications

A) **Verapamil**; 240 mg orally per day, in single or divided doses.

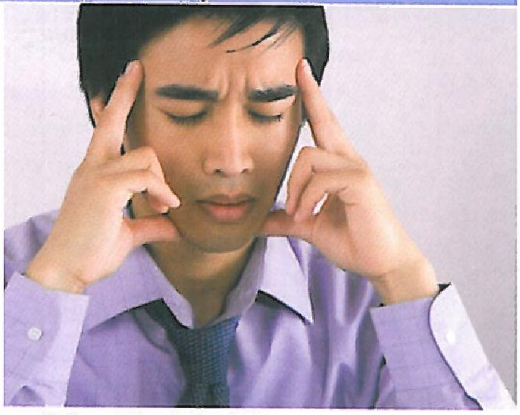
B) **Steroids**; oral **Prednisone** 50-80 mg/d, tapered gradually 10-12 days or sub-occipital injection of **Betamethasone** (used until other drug take effect).

C) **Antiepileptics**; **Valproate** and **Topiramate** are effective.

D) **Melatonin** is effective.

# Other Types of Headache

## New Daily Persistent Headache (NDPH)



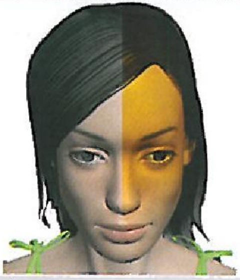
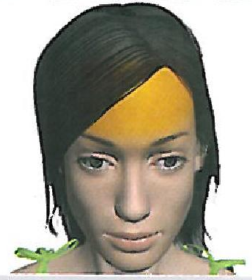
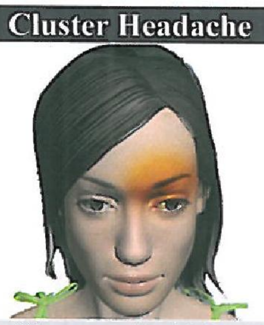
- **NDPH** is a ***primary headache***, come on ***suddenly***, ***usually*** in **people *without*** a **headache history**.
- **IHS Diagnostic Criteria**;
  - **Headache** that, ***within* 3 days** of **onset**.
  - ***Present daily***, and is ***unremitting***, for **> 3 months**.
  - ***At least* 2** of the ***following characteristics***;
    1) **Bilateral location.**
    2) **Pressing/tightening** (*non-pulsating*) **quality**.
    3) **Mild** or **moderate intensity**.
    4) ***Not* aggravated by routine physical activity.**
  - ***Both of the following***;
    - ***No* more than 1** of **photophobia**, **phonophobia** or ***mild* nausea**.
    - ***No moderate*** or ***severe*** **nausea** or **vomiting**.
- ***About* 30%** of **patients**, the ***onset*** of the **headache *occurred with*** an **infection** or **flu-like illness**.
- **Treatments**; ***No*** **successful treatment *for*** **NDPH**, ***most specialists*** work with the **same medications** prescribed for **chronic migraine**.

## Headache or facial pain attributed to disorders of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cranial structures

- **These types** are ***secondary headaches*** are **resolved** or **greatly improves *after*** **effective treatment** or ***spontaneous*** **remission** of the **primary disorder**.
- ***If*** the **primary disorder** is ***effectively*** **treated** or **remits *spontaneously but*** **headache *does not resolve*** or ***markedly*** **improve *after*** **1 month**, the **persisting headache** has ***other*** **mechanisms**.

Sinus Headache

# Differential Diagnosis of Headaches

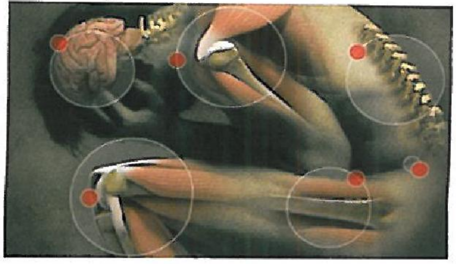
| | **Migraine** | **Tension Headache** | **Cluster Headache** |
|---|---|---|---|
| |  |  |  |
| Pain | Pulsating or Throbbing | Pressing or Tightening | Sharp or Stabbing |
| Pain Intensity | Moderate to Severe | Mild to Moderate | Severe to Very severe |
| Duration | 4 hours to 3 days | 30 min. to several days | 15-180 minutes |
| Location | Unilateral or Bilateral | Bilateral | Unilateral, eye focused |
| Aura | With or Without | Without | Without |
| Nausea/Vomiting | Very common | No | No |
| Photophobia or Phonophobia | Very common | No more than one | No (running nose and tears are common) |

- *N.B.*; **Analgesic Rebound Headache**: If patients use analgesics often (usually defined as more than three times weekly), they may develop analgesic rebound headache. Patients with this condition usually present with a chronic daily headache, for which they take simple or narcotic analgesics. Treatment consists of the withdrawal of all analgesics (but not prophylactic medications).

# Opioids

## ➢ Introduction:-

- **Pain** can be ***either*** **acute** or **chronic** and is a consequence of ***complex*** **neurochemical processes** in the **peripheral** and **central nervous systems** (CNS).
- An **analgesic** or **painkiller** is any member of the group of drugs used to ***achieve*** **analgesia**, ***relief from*** **pain**. *Analgesic choice* is also ***determined by*** the **type of pain**, ***for example***;
  - **Mild** to **moderate pain**; **Simple** (non-opioid) **analgesics** ***such as*** **nonsteroidal anti-inflammatory drugs** (**NSAIDs**) are ***often*** **effective**.
  - **Neuropathic pain**; **Responds *best*** to **anticonvulsants** and **tricyclic antidepressants**.
  - **Severe** or **chronic malignant** or **non-malignant pain**; **Opioid analgesics** are considered ***part*** of the **treatment plan** in *select patients*.

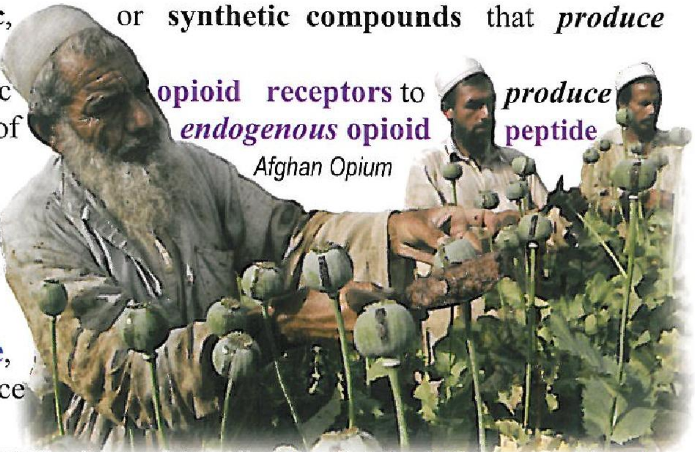


- **Major Classes of Analgesics**;
  - ***NSAIDs*** and **Paracetamol**; see NSAIDs chapter
  - ***Opioid Analgesics***; ***Agents*** that **produce morphine-like effect**.
  - ***Specific agents***; **Anticonvulsants**, **tricyclic antidepressants** and **Flupirtine** ($K^+$ channel opener with weak NMDA antagonist).

# Opioid Analgesics

## ➢ Definitions:-

- **Opioids**; are **natural**, **semisynthetic**, or **synthetic compounds** that ***produce*** **morphine-like effects**.
- **All opioids *act by* binding to** specific **opioid receptors** to ***produce effects*** that mimic the action of ***endogenous* opioid peptide** **neurotransmitter** (**Endorphins**, **Dynorphins** and **Enkephalins**).
- **Opium**; is the ***dried* latex *obtained from*** the **opium poppy** (***Papaver somniferum***).
- **Opium latex**; contains **Morphine**, which may used chemically to produce **Heroin** and ***other*** **opioids**.



Afghan Opium

- *The term* "**opioid**" originated in the 1950s. It combines "**opium**" + "**-oid**" meaning "***opiate-like***" ("opiates" being morphine and similar drugs).
- **Narcotic**; derived from words meaning ***numbness*** or ***sleep***, is ***now*** a **legal term** that ***refers to*** **opioids**.

- **Spinal analgesia**; analgesia in spinal cord and dorsal root ganglia-substantia gelatinosa.
- **Supraspinal analgesia**; analgesia in periaqueductal/periventricular gray matter in brain.

## ➢ Opioid Receptors:-

- **Opioid receptors** are a group of ***inhibitory*** **G protein-coupled receptors**;

| Receptor | Subtype | Function | |
|---|---|---|---|
| **μ (Mu)** | **μ1, μ2, μ3** | * Supraspinal analgesia$^{+++}$<br>* Physical dependence$^{+++}$<br>* Euphoria$^{+++}$<br>* Decrease GI motility$^{++}$ | * Spinal analgesia$^{++}$<br>* Respiratory depression$^{+++}$<br>* Miosis$^{++}$<br>* Sedation$^{++}$ |
| **δ (Delta)** | **δ1, δ2** | * Supraspinal analgesia$^{+}$<br>* Respiratory depression$^{++}$ | * Spinal analgesia$^{++}$<br>* Decrease GI motility$^{++}$ |
| **κ (Kappa)** | **κ1, κ2, κ3** | * Supraspinal analgesia$^{+}$<br>* Dysphoria & hallucinations$^{+++}$<br>* Sedation$^{++}$ | * Spinal analgesia$^{+}$<br>* Miosis$^{+}$<br>* Decrease GI motility$^{+}$ |

## Strong Agonists

| | | |
|---|---|---|
| **Morphine** (MS Contin®) | **Hydromorphone** (Dilaudid®) | **Oxymorphone** (Opana®) |
| **Heroin** | **Methadone** (Dolophine®) | **Meperidine** (Demerol®) |
| **Fentanyl** (Duragesic®) | **Alfentanil** (Alfenta®) | **Sufentanil** (Sufenta®) |
| **Remifentanil** (Ultiva®) | | |

- **Morphine** [MOR-feen] is the ***major*** **analgesic drug**, it is a ***natural*** **compound** ***found*** in **crude opium** and is the ***prototype*** **strong μ receptor agonist**.
- **Hydromorphone** [HYE-droe-MOR-fone] is a ***semi-synthetic*** **Morphine** ***derivative***, is ***much more*** **water** ***soluble*** than **Morphine**.
- **Oxymorphone** [ox-ee-MOR-fone] is a ***semi-synthetic*** **Morphine** ***derivative***, is ***more*** **lipid** ***soluble*** than **Morphine**, resulting in a ***rapid onset of action*** when given in oral route.
- **Heroin** [HEE-ro-in] **Diamorphine** or **Diacetylmorphine** is a ***semi-synthetic*** **Morphine** ***derivative***, by adding ***two*** **acetyl groups** to **Morphine**, is ***stronger than*** **Morphine**.
- **Methadone** [METH-a-done] and **Meperidine** [me-PER-ih-deen] or **Pethidine** are a ***synthetic*** **opioid analgesics, structurally** ***unrelated*** to **Morphine**.
- **Fentanyl** [FEN-tuh-NILL] is a ***potent*** (80-100 times ***more potent than*** **Morphine**), ***synthetic*** **opioid analgesic** with a ***rapid*** **onset** and ***short*** **duration of action**.
- **Alfentanil** [al-FEN-tuh-NILL], **Sufentanil** [soo-FEN-tuh-NILL] and **Remifentanil** [rem-ih-FEN-tuh-NILL] are ***synthetic*** **opioid**, **Fentanyl** ***structural analogues***.

## Mild to Moderate Agonists

| | | |
|---|---|---|
| **Codeine** | **Hydrocodone** (Lortab®) | **Oxycodone** (Oxycontin®) |

- **Codeine** [KOE-deen] (**3-Methyl-Morphine**) is a ***natural*** **opioid alkaloid** ***found in*** the **opium poppy**, it is a ***weak opioid agonist***.
- **Hydrocodone** [HYE-droe-KOE-done] is a ***semi-synthetic*** **Codeine** ***derivative***, is ***stronger than*** **Codeine** (about 50%). **Oxycodone** [ok-see-KOE-done] is a ***semi-synthetic*** **Codeine** ***derivative***, is ***stronger than*** **Hydrocodone** (about 50%).

## Partial Agonists and Mixed Agonist-Antagonist

| | |
|---|---|
| **Buprenorphine** (Subutex®) | **Pentazocine** (Talwin®) |
| **Nalbuphine** (Nubain®) | **Butorphanol** (Stadol®) |

- **Buprenorphine** [byoo-pre-NOR-feen] is a ***partial agonist***, at **μ receptor**, and ***antagonist*** at **κ & δ**.
- **Pentazocine** [pen-TAZ-oh-seen] is a ***mixed agonist-antagonist***, acts as an ***agonist*** on **κ receptors** and is a ***weak antagonist*** at **μ receptors**.
- **Nalbuphine** [NAL-byoo-feen] is a ***mixed agonist-antagonist***, acts as an ***agonist*** on **κ receptors** and is an ***antagonist*** at **μ receptors**.
- **Butorphanol** [byoo-TOR-fa-nole] is a ***mixed agonist-antagonist***, acts as an ***agonist*** on **κ receptors** and is an ***antagonist*** or ***partial agonist*** at **μ receptors**.

## Other Opioid Analgesics

| | |
|---|---|
| **Tramadol** (Contramal®) | **Tapentadol** (Nucynta®) |

- **Tramadol** [TRA-ma-dole] is a **μ receptor** ***agonist*** & **norepinephrine/serotonin reuptake** ***inhibitor***.
- **Tapentadol** [ta-PEN-ta-dol], is a **μ receptor** ***agonist*** and **norepinephrine reuptake** ***inhibitor***.

## Other Opioids Not Used as Analgesics

| | | |
|---|---|---|
| **Dextromethorphan** | **Diphenoxylate** | **Loperamide** (Imodium®) |

- **Dextromethorphan** [deks-troe-meth-OR-fan] is an ***antitussive*** **opioid derivative**.
- **Diphenoxylate** [dye-fen-OX-i-late] & **Loperamide** [loe-PER-a-mide] are an ***antidiarrheal*** **opioids**.

## Opioid Antagonists

| | | |
|---|---|---|
| **Naloxone** (Narcan®) | **Naltrexone** (Anarcol®) | **Nalmefene** (Revex®) |

- **Naloxone** [nal-OX-own], **Naltrexone** [nal-TREX-own] and **Nalmefene** [NAL-me-feen].

## ➢ Characteristics of the main opioid analgesic drugs:-

| Drug | Receptor Effects$^1$ | | | Usual Routes | Usual Dose (mg) | Duration (h) | Agonist Efficacy |
|---|---|---|---|---|---|---|---|
| | μ | δ | κ | | | | |
| **Morphine** | +++ | | + | Oral$^2$, Injection | 10 | 4-5 | High |
| **Hydromorphone** | +++ | | | Oral, Injection | 1.5 | 4-5 | High |
| **Oxymorphone** | +++ | | | Oral, Injection | 1.5 | 3-4 | High |
| **Methadone** | +++ | | | Oral, Injection | 10 | 4-6 | High |
| **Meperidine** | +++ | | ++ | Oral, Injection | 60-100 | 2-4 | High |
| **Fentanyl** | +++ | | | IV, Patches, Intranasal, Lozenges | 0.1 | 1-1.5 (IM)<br>0.5-1 (IV) | High |
| **Sufentanil** | +++ | + | + | IV, Patches | 0.02 | 1-1.5 | High |
| **Alfentanil** | +++ | | | IV | Titrated | 0.25-0.75 | High |
| **Remifentanil** | +++ | | | IV | Titrated | 0.05 (3 min.) | High |
| **Oxycodone** | ++ | | | Oral, Injection | 4.5 | 3-4 | Mod-High |
| **Hydrocodone** | + | | | Oral, Injection | 5-10 | 4-6 | Moderate |
| **Codeine** | / | | | Oral | 30-60 | 3-4 | Low |
| **Buprenorphine** | ± | -- | -- | Sublingual, Patches, Injection | 0.3 | 4-8 | Moderate |
| **Pentazocine** | - | | + | Oral, Injection | 30-50 | 3-4 | Moderate |
| **Nalbuphine** | -- | | ++ | Injection | 10 | 3-6 | High |
| **Butorphanol** | ± | | +++ | IV, intranasal, oral | 2 | 3-4 | High |

1; +++, ++, +; strong agonist, / weak agonist, ±; partial agonist, -,--; antagonist.
2; Available in sustained-release.

## Morphine

### Morphine (MS Contin®)

- **Morphine** (*prototype*) is a **phenanthrene** (*chemical class*) ***strong*** **μ receptor** ***agonist***.

**Pharmaco Kinetics**

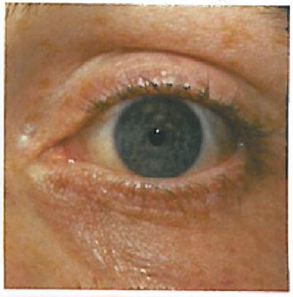
- ***Absorption***; **Oral absorption** of **Morphine** from the **GI tract** is *slow*, and subject to ***extensive*** **first-pass metabolism**, so the **oral dose** need to be ***much higher than*** the **parenteral dose** (***Bioavailability***; about 30%).
- ***Administration***; **Morphine** can be taken **orally**, **parenterally** (IV, SC, IM and intrathecally), **rectally** or **intranasally**. **Morphine** is ***commonly*** **administered medically** in an **oral** ***extended-release*** (***consistent*** **plasma levels**) and **IV injection**.
- ***Distribution***; **Morphine** ***rapidly*** **enters all body tissues**, including **placenta**. ***Only*** a **small amount** of **Morphine** ***crosses*** the **BBB**, ***because*** **Morphine** is the ***least*** **lipophilic** of the **common opioids**.
- ***Metabolism***; **Morphine** is ***conjugated*** with **glucuronic acid** in the **liver** to ***two*** **main metabolites** (***excreted*** in **urine**, with ***small amount*** in **bile**);
  1) **Morphine-6-glucuronide (M6G)** (about 10%) is a ***very*** **potent analgesic** (4 to 6 times more than **Morphine**).
  2) **Morphine-3-glucuronide (M3G)** does ***not*** have **analgesic activity**, but is believed to cause the **neuroexcitatory effects**.

## Mechanism OF Action

- **Morphine** and *other* **opioids** *stimulates* specific **opioid receptors**.
- *Stimulation* of **opioid receptors** in the **CNS** *decreases* **release** of **substance-P** (which *responsible* for **pain transmission in spinal cord**).
- *All* **opioid receptors** are *coupled* to *inhibitory* **G-protein** that *leads to* $K^+$ **channels** *activation* and $Ca^{2+}$ **channels** *inhibition* this leads to *hyperpolarization* of **nerve cell**.
- *Inhibition* of **nerve cell** *leads to decrease* **release** of **excitatory neurotransmitters**.

## Pharmacological Action

1) **Analgesia** (*relief* **pain** *without* **loss of consciousness**) by;
   - *Raising* the **pain threshold** at the **spinal cord**.
   - *Altering* the **brain's perception** of **pain**.
2) **Euphoria**;
   - **Morphine** *produces* a *powerful* **pleasant sensation** (*sense of* **contentment** and **well-being**).
   - **Dysphoria**, an *unpleasant state* characterized by **restlessness** & **malaise**, may **occur** (not in pain).
3) **Sedation**;
   - **Drowsiness** are *common* effects of opioids.
   - **Morphine** *disrupts* normal **rapid eye movement** (**REM**) and *non*-**REM** sleep patterns.
4) **Respiratory Depression**;
   - *All* **opioids** *can* produce *significant* **respiratory depression** by *inhibiting* **respiratory centres** in the **brainstem** (*reduce* **sensitivity** of the **brain stem** to **carbon dioxide**).
   - **Respiratory depression** is the *most common* cause of **death** in *acute* **opioid overdoses**.
5) **Cough Suppression**;
   - *Both* **Morphine** and **Codeine** have **antitussive properties** (**Codeine** has *lesser* **analgesic activity**).
   - **Cough suppression** by **opioids** may allow *accumulation* of **secretions** and thus *lead to* **airway obstruction**.
6) **Emesis**;
   - **Opioid analgesics** can *activate* brainstem **chemoreceptor trigger zone** (**CTZ**) to *produce* **nausea** and **vomiting**.
7) **Miosis**;
   - **Opioids** *stimulate* μ & κ receptors at **Edinger-Westphal nucleus** of **oculomotor nerve** to *constrict* the **pupil** causing **miosis** which is called ☞ **Pinpoint pupil** (**PPP**).
   - This is *important* **diagnostically** for **physicians** or **policemen**.



- *Most* **opioids** have *no significant* **direct effects** on the **heart rate** or **blood pressure**.
- With **large doses**, **hypotension** and **bradycardia** (**Meperidine** is an *exception* can cause **tachycardia**).
- **Hypotension**; due to *vasodilatation* due to 1) *release* of **histamine** & 2) *depression* of **vasomotor center** (**VMC**).
- *N.B.*; *Because of* **respiratory depression** and **carbon dioxide retention**, **cerebral vessels** *dilate* and *increase* **cerebrospinal fluid pressure** (*see contraindications*).

## Pharmacological Action

- *Decrease* **GI motility** (**peristalsis**), ***leads to*** **constipation**.
- *Increase* **GI tone** (contraction of circular smooth muscle).
- **Biliary colic**, due to biliary smooth muscle contraction.
- *Decrease* **renal function** (***enhance*** **renal tubular sodium** *reabsorption* and *increase* **antidiuretic hormone** (ADH) *release*).
- *Increase* **ureteral** and **bladder tone**.
- *Increase* **sphincter tone** (**urinary retention**).
- **Opioids** *may* **prolong labor**.
- *Stimulate* **release** of **antidiuretic hormone** (**ADH**), **prolactin**, and **somatotropin** (**growth hormone**; **GH**)
- *Inhibit* **release** of **luteinizing hormone** (**LH**).
- **Pruritus**; **Flushing** and **skin warming** with **itching** *due to* **central effects** and peripheral **histamine release**.

## Therapeutic Uses

### * Clinical Use of Opioid (Morphine and *other opioids*) Analgesics *

1) **Analgesia** (***relief*** **pain** ***without*** **loss of consciousness**);
   - *Moderate* to *severe* ***constant*** **pain** that does not respond to non-opioids analgesics alone. Examples;
   - *Acute* **pain**; Myocardial infarction (MI), trauma, postoperative pain, surgery, burns, renal colic, biliary colic and acute abdominal pain.
   - *Chronic* **pain**; Cancer pain & some types of chronic non-cancer pain (CNCP).
   - *Labour pain*, Because opioids cross the placenta, The phenylpiperidine drugs (e.g. **Meperidine**) appear to produce less depression in newborn infants than **Morphine**.
2) **Acute Pulmonary Edema**;
   - IV **Morphine** may use in **dyspnea** from **pulmonary edema** ***associated with*** **left ventricular heart failure**, due to ***reduced*** **anxiety** (perception of shortness of breath) and ***reduced*** **cardiac preload** (reduced venous tone) and ***reduced*** **afterload** (decreased peripheral resistance).
   - **If respiratory depression** is a ***problem***, **Furosemide** may be ***preferred***.
3) **Cough Suppression**;
   - Cough suppression obtained at **doses *lower than*** those needed for **analgesia**.
   - **Synthetic compounds** (**Dextromethorphan**) have been developed that are not analgesic and not addictive.
4) **Diarrhea**;
   - **Synthetic compounds** (**Diphenoxylate** and **Loperamide**) ***more selective*** **gastrointestinal effects** and ***few*** or ***no*** **CNS effects**.
5) **Preanesthetic Medication**;
   - **Opioids** are ***frequently*** **used** as **drugs *before* anesthesia** and **surgery *because*** of their **sedative**, **anxiolytic** and **analgesic properties**.

## Side Effects

1) **Tolerance**;
   - ***Development*** of **tolerance *begins with*** the **first dose**, but ***become*** **clinically manifest *after*** **2-3 weeks** of ***frequent*** **exposure**.
   - **Tolerance** to the **respiratory depressant**, **analgesic**, **euphoric**, **sedative**, **antidiuretic**, **emetic** and **hypotensive effects**.
   - **Tolerance** usually does ***not*** **develop** to the **pupil-constricting** and **constipating effects**.
   - **Cross-tolerance**; *example*, **patients *tolerant to*** **Morphine** are also ***tolerant to other*** **agonist opioids**.

## Side Effects

**2) Dependence;**

- **Drug dependence** and ***severity*** of **withdrawal effects** are ***depend on*** **compound** and **differences** *between* the **various opioids**, *example* ***withdrawal*** **signs** and **symptoms** *from* **strong agonist** is associated with ***more severe than*** **withdrawal** from a **mild** or **moderate agonist**.
- **Opiate withdrawal symptoms** and **managements** ***seen*** **later**, after opioid drugs discussion.

**3) Acute Side Effects; Respiratory depression, nausea, vomiting, allergic reactions, bronchoconstriction** and **constipation.**

## Contra indication

**1) Combination of *full* agonists** with ***weak*** **partial agonists;**

- Combination of ***weak*** **partial agonist** such as Pentazocine with ***full*** **agonist** such as Morphine ***should be*** **avoided**, there is a ***risk*** of ***diminishing*** **analgesia** or ***inducing*** a **state of withdrawal**.

**2) Head Injuries;**

- *Because of* **respiratory depression** and **carbon dioxide retention** ⇨ **cerebral vessels** ***dilate*** and ***increase*** **cerebrospinal fluid pressure**, ⇨ ***elevated*** **intracranial pressure** ⇨ ***lethal*** **alterations** in **brain function**.

**3) Pregnancy;**

- **Fetus** may become **physically dependent** in utero and manifest ***withdrawal symptoms*** (irritability, shrill crying, diarrhea, or even seizures) in the ***early*** **postpartum period**.

**4) Impaired Pulmonary Function;**

- The **respiratory depressant** ***effects*** of the **opioid analgesics** may ***lead to*** **acute respiratory failure**.

**5) Liver Failure and Kidney Failure.**

**6) Endocrine Disease;**

- **Adrenal insufficiency** (**Addison's disease**) and those with **hypothyroidism** may have ***prolonged*** and ***exaggerated*** **responses** to **opioids**.

**7) Benign Prostatic Hyperplasia (BPH);**

- **Opioids** ***decrease*** **renal function** and may cause **urinary retention**.

*** Most of opioids are listed as Schedule II drugs ***

## Specific Agents

## Strong Agonists

### Phenanthrenes

### Hydromorphone (Dilaudid®)

- **Hydromorphone** is a ***semi-synthetic*** **Morphine** ***derivative***, is ***hydrophilic like***, ***more*** **water soluble** ***than*** **Morphine**.
- ***Oral*** **Hydromorphone** (*usual oral dose* 1.5 mg) is *approximately* **8-10 times** ***more potent*** than **Morphine** (*usual oral dose* 10 mg).
- ***Extended-release*** (*once-daily*) **formulation** of **Hydromorphone** (Exalgo®) is *available*.
- **Hydromorphone** is ***extensively*** **metabolized** in the liver to **morphine-3-glucuronide** (**M3G**) (>95%), which has ***no*** **analgesic activity**, can ***produce*** **excitatory neurotoxic**.
- **Morphine** are ***contraindicated*** in **renal failure**, while **Hydromorphone** is **used** ***with caution***.

### Oxymorphone (Opana®)

- **Oxymorphone** is a ***semi-synthetic*** **Morphine** ***derivative***, is ***more*** **lipid** ***soluble*** than **Morphine**, resulting in a ***rapid onset of action*** when given in **oral route**.
- **Oxymorphone**, ***Parenterally***; *approximately* **10 times** ***more potent*** than **Morphine**.
  ***Orally***; *approximately* **3 times** ***more potent*** than **Morphine**.
- ***Extended-release*** (*once-daily*) **formulation** of **Oxymorphone** (Opana® ER) is *available*.

## Heroin

- **Heroin** [HEE-ro-in] **Diamorphine** or **Diacetylmorphine** is a ***semi-synthetic*** **Morphine** ***derivative***, by adding ***two*** **acetyl groups** to **Morphine**.
- **Heroin**, ***Parenterally***; *approximately* is **2-4 times *more potent*** than **Morphine** and is ***faster*** in its **onset of action**.
- **Heroin** is ***rapidly*** **hydrolyzed** into **6-monoacetylmorphine (6-MAM)** and **Morphine**.
- **Illicit Heroin** is available in a **matte-white powder**.
- ***Routes of illicit*** **Heroin** ***administration***;
  - ***Injection***; **Is a *popular route*, Heroin** powder, is ***dissolved*** in **water *mixed*** with an **acid (citric acid powder** or **lemon juice)** and ***heated*** in **aluminium foil** or **spoon** by ***using*** **lighter** or **flame source**, **share needle** is a ***risk for*** blood-borne diseases, such as **HIV** or **hepatitis**, **Tropicamide** (***antimuscarinic***) containing **eyedrops**, ***used to*** produce ***short-acting*** **mydriasis** and **cycloplegia** is ***currently*** **abused**, as an ***inexpensive*** **euphoric deliriant drug**. It is usually ***mixed*** with **Heroin** and ***other*** **opioids** to ***increase*** the **efficacy** and ***decreasing*** or ***delaying*** the **withdrawal symptoms**.
  - ***Insufflation*** (***snorting***); ***Fine powder*** is gently **inhales** into the **nose**, by ***using*** **tube** of **paper money**.
  - ***Smoking***; **Heroin** has ***lower*** **boiling point**, ***powder*** of **Heroin** is ***placed*** in **aluminium foil**, ***using gentle*** **heat** from a **lighter** or **flame source** ***to*** **vaporization**, by ***using*** the **funnel tube**, **Heroin smoke** is ***inhaled***.

FARBENFABRIKEN vorm.
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ELBERFELD
Heroin

- The ***withdrawal syndrome*** from **Heroin** may begin ***within*** **6-24 hours** of ***discontinuation***.
- In **2004**, **Afghanistan** accounted for ***production*** of **87%** *of the* **world's Heroin**, **Afghan opium *kills*** around **100,000 people *annually***.
- In **1898**, the German drug company **Bayer** marketed **Diacetylmorphine** as an over-the-counter (**OTC**) **drug** under the **trademark** name Heroin®.
- The name was derived from the **Greek word "heros"** because of its perceived **"heroic" effects** upon a user.
- It was ***developed as*** a **Morphine *substitute*** for **cough suppressants** that did not have **morphine's *addictive* side-effects**!! , but **Heroin** would soon have one of the ***highest rates*** of **addiction** among its users, it is ***now*** a **Schedule I substance**.

## Phenylheptylamines

### Methadone (Dolophine®)

- **Methadone** is a ***synthetic*** **opioids**, **structurally *unrelated*** to **Morphine**.
- ***Pharmacokinetics***;
  - ***Routes***; **Oral**, **IV**, **SC**, **spinal**, and **rectal** routes.
  - ***Absorption***; It is ***well absorbed*** from the **GIT**.
  - ***Distribution***; It is ***very*** **lipophilic**, leading to ***accumulation*** in the **fat tissues**, (***long*** **half-life; 25-52 hours**).
  - ***Metabolism***; In the **liver** by **demethylation** and **cytochrome P450 enzymes**, ***used with*** **caution** in **hepatic dysfunction**.
  - ***Excretion***; ***Almost*** in **feces** (***safe*** to use in **renal failure**).
- ***Mechanism of Action***; It is ***not only*** a ***potent*** **μ-receptor agonist** but it can also ***block*** **NMDA receptors** and **norepinephrine** and **serotonin reuptake *inhibitor***.
- ***Uses***;
  - **Pain** (**neuropathic pain** is ***included*** due to ***non*-opioid mechanisms**).
  - **Control withdrawal symptoms** of **opioid dependency** (**Methadone Maintenance Treatment**; **MMT**, *see withdrawal symptoms*), induced ***less*** **euphoria**, **tolerance** & **physical dependence** develop ***more slowly*** & **withdrawal symptoms** are ***milder*** than **Morphine**.
- ***N.B.***;
  - **Methadone** can ***prolong*** the **QT interval**.
  - **Methadone** overdose can ***cause*** **respiratory depression**.

## Phenylpiperidines

### Meperidine or Pethidine (Demerol®)

- **Meperidine** or **Pethidine** is a ***synthetic*** **opioid, structurally** ***unrelated*** to **Morphine**, but ***related*** to **Atropine**, it is ***very*** **lipophilic** and has ***anticholinergic effects***, ***increased*** **incidence** of **delirium**.
- It is ***metabolized to*** an **active metabolite Normeperidine** (***neurotoxic*** and ***serotonergic effects***).
- It is a **κ *agonist*** and also has **local anesthetic *effects***.
- It is the ***preferred*** **opioid** in *some countries* ***used*** in **labour** and **delivery**.
- *Due to* **anticholinergic effects**, It is preferred in **pain *associated with*** **biliary spasm** or **renal colic**.
- **Serotonin syndrome** has also been ***reported*** in patients receiving both **Meperidine** and **SSRIs**.

### Fentanyl (Duragesic®)

- **Fentanyl** is **one** of the ***most widely synthetic opioids*** **used**.
- It is *approximately* **80-100 times *more* potent *than* Morphine** and *approximately* **40-50 times *more* potent *than* Heroin**, it is ***highly*** **lipophilic** and has a ***rapid*** **onset** and ***short*** **duration** of **action**.
- ***Common Routes and Formulations***;
  - ***IV injection***; ***duration***; 30-60 minutes, ***used for*** **adjunct *to an*** **anaesthetic** (**analgesic** and **sedative effects**) and **analgesia** for ***moderate*** and ***severe*** **pain**.
  - ***Transdermal patch***; ***duration***; 72 hours, ***used for*** **chronic pain**.
  - ***Transmucosal***; **Fentanyl lozenges** (Actiq®), ***duration***; 1-2 h, ***used in*** **breakthrough pain** (*sudden flare of pain*), e.g. **breakthrough cancer pain** (**BTCP**), **nasal spray**, **sublingual spray**, **sublingual tablets** and **buccal tablets** are **transmucosal *drug delivery*** and are also ***available*** and ***used*** in **breakthrough pain**.
- **Fentanyl** may **produce *more prolonged*** **respiratory depression** than other opioid analgesics, (*especially* **Fentanyl skin patches**).
- **Fentanyl** is ***metabolized to*** **inactive metabolites** by the **CYP3A4**, **CYP3A4 *inhibitors*** can ***potentiate*** **Fentanyl effects**. ***Inactive*** **metabolites** are ***eliminated*** **renally**.
- **Fentanyl** appears to be ***safe*** to ***use in*** **renal failure**.

### Alfentanil (Alfenta®) | Sufentanil (Sufenta®) | Remifentanil (Ultiva®)

- **Alfentanil**, **Sufentanil** and **Remifentanil** are ***synthetic*** **opioid**, **Fentanyl *structural analogues***.
- **Alfentanil** an ***ultra-short acting***, **Sufentanil**, a ***potent analgesic*** (5-10 times more potent than **Fentanyl**), **Remifentanil**, a ***shortest-acting*** **opioid**.
- **These agents** are ***mainly*** **used** for **adjunct *to an*** **anaesthetic** (analgesic and sedative effects) ***during*** **surgical procedures**. **Sufentanil** appears to be ***safe*** to ***use in*** **renal failure**.
- **Carfentanil** is a ***synthetic*** **Fentanyl *analogue***, is ***most potent*** **opioids** (approximately 10,000 times ***more potent*** than **Morphine**), used as ***general anaesthetic*** agent for ***large*** **animals**.

# Mild to Moderate Agonists

## Phenanthrenes

### Codeine

- **Codeine** [KOE-deen] (**3-Methyl-Morphine**) is a ***natural*** **opioid alkaloid** (*about* 2% of opium) and is a ***weak opioid agonist***. **Codeine** is ***converted to*** **Morphine** by the **CYP2D6 enzyme** in the liver.
- It is *typically* ***used*** to ***treat*** ***mild*** to ***moderate*** **pain**, and ***commonly*** used in ***combination with*** **Paracetamol** (Tylenol® No.3) or **Aspirin** (Co-codaprin®).
- **Codeine** exhibits ***good antitussive activity*** at **doses** that ***do not cause*** **analgesia** (**evidence *does not support*** its **use *for*** **cough suppression**).

### Hydrocodone (Lortab®) | Oxycodone (Oxycontin®)

- **Hydrocodone** and **Oxycodone** are ***semi-synthetic*** **Codeine *derivative***. **Hydrocodone** is ***stronger than*** **Codeine** (about 50%), while **Oxycodone** is ***stronger than*** **Hydrocodone** (about 50%).
- **Hydrocodone** and **Oxycodone** are used to treat ***moderate*** to ***severe*** **pain**, and ***sometimes*** used in ***combination with*** **NSAIDs**. ***Extended release*** **formulations** are available.
- **Hydrocodone** ***also used*** as an **antitussive**.

# Partial Agonists and Mixed Agonist-Antagonist

## Phenanthrenes

### Buprenorphine (Subutex®)

- **Buprenorphine** is a ***partial agonist***, at **μ receptor**, and ***antagonist*** at **κ** & **δ**.
- It **cause** ***mild*** **withdrawal symptoms** and ***little*** **sedation, respiratory depression** or **hypotension** ***even at*** **high doses** (*advantage over* **Methadone**), so it is ***widely used*** to ***treat*** **opioid addiction** (**opioid detoxification**) or **opioid dependence**, and may ***use*** to treat ***moderate*** to ***severe*** **pain**,
- ***Routes of administration***; **Injection** and **transdermal patch** are ***indicated for*** **pain**, while **sublingual tablet** is ***indicated for*** **opioid dependence.**
- **Buprenorphine** also **available** in a ***combination with*** **Naloxone** (***opioid antagonist***) (Suboxone®) at a 4:1 ratio, **sublingual tablet** is ***used*** for **opioid dependence** (*see withdrawal symptoms*).

### Nalbuphine (Nubain®)

- **Nalbuphine** is a ***mixed agonist-antagonist***, ***agonist*** on **κ receptors** and ***antagonist*** at **μ receptors.**
- It is ***used*** **parenterally** ***for***; ***moderate*** to ***severe*** **pain**, ***supplement*** to **balanced anesthesia** (preoperative and postoperative analgesia), and **obstetrical analgesia** (during labor and delivery).

## Morphinans

### Butorphanol (Stadol®)

- **Butorphanol** is a ***mixed agonist-antagonist***, ***agonist*** on **κ receptors** and ***antagonist*** or ***partial agonist*** at **μ receptors.**
- It ***produces*** **analgesia** ***equivalent to*** **Nalbuphine** & **Buprenorphine** ***but*** it ***produce more*** **sedation.**
- **Butorphanol intranasal spray** is ***indicated for*** **migraine, Butorphanol injection** is ***indicated for moderate*** to ***severe*** **pain**, ***supplement*** to **balanced anesthesia** and **obstetrical analgesia.**

## Benzomorphans

### Pentazocine (Talwin®)

- **Pentazocine** is a ***mixed agonist-antagonist***, **κ receptor** ***agonist*** & ***weak*** **μ receptor** ***antagonist.***
- **Pentazocine injection or oral** ***alone*** (Talwin®) or **oral** ***combination with*** **Naloxone** (Talwin® NX) (**Naloxone** not absorbed orally *but* used to prevent drug abuse if injected), is ***indicated for moderate-severe*** **pain**, ***supplement*** to **balanced anesthesia** & **obstetrical analgesia.**
- ***High*** **doses** ***increase*** **blood pressure** and can cause **hallucinations** (**psychotomimetic** ***effects***; due to its ***action*** at the **κ receptors**).
- **Pentazocine should** be ***used with*** **caution** in ***patients with*** **coronary artery disease.**

# Other Opioid Analgesics

### Tramadol (Contramal®)

- **Tramadol** is a **μ receptor** ***agonist*** and **norepinephrine/serotonin reuptake** ***inhibitor.***
- It is ***metabolized by*** **CYP2D6, CYP3A4** and **CYP2B6,** ***leading to*** an **active metabolites** with a ***much higher*** **affinity** for the **μ receptor** than **Tramadol, metabolites** are ***eliminated*** *primarily* by the kidneys (**dose** ***reduction*** **in renal** and **hepatic** ***impairment***).
- ***Mechanism of Action***; 1) ***Weak*** **μ-receptor agonist** 2) ***Weak*** **norepinephrine & serotonin inhibitor**
- It is ***used for*** **moderate** to **moderately severe** **pain**, for ***severe pain*** it is ***less*** **effective** than **Morphine.**
- Its **respiratory depressant** ***activity*** and **constipation** is ***less than*** that of **Morphine.**
- ***Toxicity*** of **Tramadol** are ***associated with*** **seizures** (***contraindicated*** in **patients with a history** of **epilepsy** and for use with ***other*** **drugs** that ***lower*** the **seizure threshold**).
- ***Risk*** of ***serotonin syndrome***, are ***increased*** *especially* if **selective serotonin reuptake inhibitor** (**SSRI**) **antidepressants** are ***co-administration*** with **Tramadol.**
- **Tramadol** has been ***associated with misuse*** (***delay*** **ejaculation** and **wakefulness**) and ***abuse.***
- ***Long***-**term use** of ***high*** **doses** of **Tramadol** will ***cause dependence*** and a ***withdrawal syndrome.***
- **Tramadol** and ***active*** **metabolites** may be ***detected*** in the **blood** to ***monitor for*** **abuse.**
- ***Fatalities*** with **Tramadol** ***overdose*** *have been* **reported.**
- ***In 2014***, **Tramadol** has been ***placed into*** **Schedule IV.**

### **Tapentadol** (Nucynta®)

- **Tapentadol** is a ***newer*** **analgesic** was ***approved by*** **FDA** in **2008**.
- ***Mechanism of action***; ***modest*** **μ receptor** ***agonist***, ***significant*** **norepinephrine reuptake** ***inhibitor*** (NRI), and ***weak*** **effects** on **serotonin reuptake**.
- ***Metabolism***; **Tapentadol metabolites** are ***inactive***.
- It is ***used for moderate*** to ***severe*** **pain**, it is also ***indicated for*** **diabetic neuropathy pain** (NRI).
- **Tapentadol** carries ***risk for seizures*** and for the ***development of serotonin syndrome***.
- ***In 2015***, Nucynta® ***annual sales*** are $166 million.
- **Tapentadol** ***not*** be **placed** ***under*** **international control** ***but*** **remain** ***under*** **surveillance**.
- ***Black box warning***; ***May cause serious, life-threatening*** **respiratory depression** and ***risk for*** **addiction, abuse** or **misuse**.

## Other Opioids Not Used as Analgesics

### **Dextromethorphan**

- **Dextromethorphan** (**DXM** or **DM**) is the ***dextrorotatory*** enantiomer of **Levomethorphan**, which is the ***methyl ether*** of **Levorphanol**, ***both*** **opioid analgesics**.
- It is ***free*** of **addictive properties** and produces ***less*** **constipation** than **Codeine**.
- It is ***one*** of the **active ingredients** in ***many*** **over-the-counter (OTC) cold** and **cough medicines**.
- The ***primary use*** of **Dextromethorphan** is as a **cough suppressant** (*antitussive*).
- ***Usual antitussive dose*** is **15-30 mg 3** or **4 times** ***daily***.
- At ***high*** **doses Dextromethorphan** acts as an **NMDA receptor** ***antagonist*** (**Hallucinations**).
- ***In 2010***, the **FDA approved** the ***combination*** product **Dextromethorphan/Quinidine** for the treatment of **Pseudobulbar affect (PBA)** (***emotional mismatch***), is a **neurological disorder** *characterized by* ***involuntary*** **crying** or **uncontrollable episodes** of **crying** and/or **laughing**, or other **emotional displays**, it occurs ***secondary*** to a **neurologic disease** such as **multiple sclerosis** or **brain injury**.
- It is ***should*** not be taken with **MAO inhibitors** due to the ***potential for*** **serotonin syndrome**.

### **Diphenoxylate**

- **Diphenoxylate**, is an **opioid drug** act as ***antiperistaltic drug***.
- **Diphenoxylate** ***decrease*** the **speed** and **amplitude** of ***wave-like*** **movements** of the **intestines (peristalsis)**. **Diphenoxylate** and **Atropine** (lomotil®) ***combination used*** to treat ***severe*** **diarrhea** in **adults** (*not in children*).

### **Loperamide** (Imodium®)

- **Loperamide**, is an **OTC opioid drug** act as ***antidiarrheal drug***.
- **Loperamide** is a **μ receptor** ***agonist*** on the **large intestine**.
- **Loperamide** ***does not cross*** the **BBB**, ***concurrent*** **administration** of **P-glycoprotein** ***inhibitors*** (*mechanism prevents* **Loperamide** *from crossing the BBB*) such as **Quinidine** allow **Loperamide** to cross the BBB, and may produce **respiratory depression**.
- **Loperamide** is effective for the ***treatment*** of a ***many types*** of **diarrhea** (acute nonspecific diarrhea, traveler's diarrhea, irritable bowel syndrome and chronic diarrhea in inflammatory bowel disease).
- ***Drug avoided*** in ***high*** **fever** and if **stool** is ***bloody*** or ***black***.
- It *may* ***increase*** the **risk** of **toxic megacolon** (*acute colonic distension*) and **paralytic ileus**.

# Opioid Antagonists

## Naloxone (Narcan®)

- **Naloxone** is a ***pure opioid antagonist***, it is used to ***reverse*** the **coma** and **respiratory depression** of **opioid overdose**.
- ***Onset***; ***Within*** **30 seconds** of **IV injection** of **Naloxone**, the **respiratory depression** and **coma** of **morphine high doses** are ***reversed***.
- ***Half-life***; **30-81 minutes**, ***shorter than*** the **half-life** of ***some*** **opiates**, ***repeat*** **dosing** ***may require***.
- It is *primarily* ***metabolized*** by the **liver** and ***excreted*** in the **urine**.
- ***In 2014***, the **US FDA** ***approved*** Evzio®, a **hand-held automatic injector Naloxone**, can be used in non-medical settings such as in the home.
- ***In 2015***, the **US FDA** ***approved intranasal*** **spray Naloxone**, ***easy-to-use*** to ***treat*** **opioid overdose**.
- The ***major uses*** of **Naloxone** is in the ***treatment*** of **acute opioid overdose**.
- It may be ***useful*** as an ***adjunctive agent*** in the ***management*** of **septic shock**.
- *N.B*; **Naloxone** ***cannot be*** **absorbed** ***orally***, so it is *commonly* ***combined*** with a number of oral opioids, including **Buprenorphine** (Suboxone®) and **Pentazocine** (Talwin NX®), ***so*** that when **taken orally** just the **opioid** has an **effect**; ***but*** if ***misused*** by **injecting**, the **Naloxone** ***blocks*** the **effect** of the **opioid**.

## Naltrexone (Anarcol®)

- **Naltrexone** has **actions** ***similar to*** those of **Naloxone**.
- It is ***orally active*** and has a ***longer duration*** **of action** than **Naloxone** (***single*** **oral dose** of **Naltrexone** ***blocks*** the ***effect*** of ***injected*** **Heroin** for ***up to*** **24 hours**).
- It is ***used primarily*** in the ***management*** of **alcohol dependence** (**alcoholism**, *unknown mechanism*) and **opioid dependence**. **Naltrexone** in ***combination with*** **Clonidine** (and sometimes with **Buprenorphine**) is ***used for*** **rapid opioid detoxification**.
- **Naltrexone** has been reported to cause **hepatotoxicity** (*dose-dependent*).

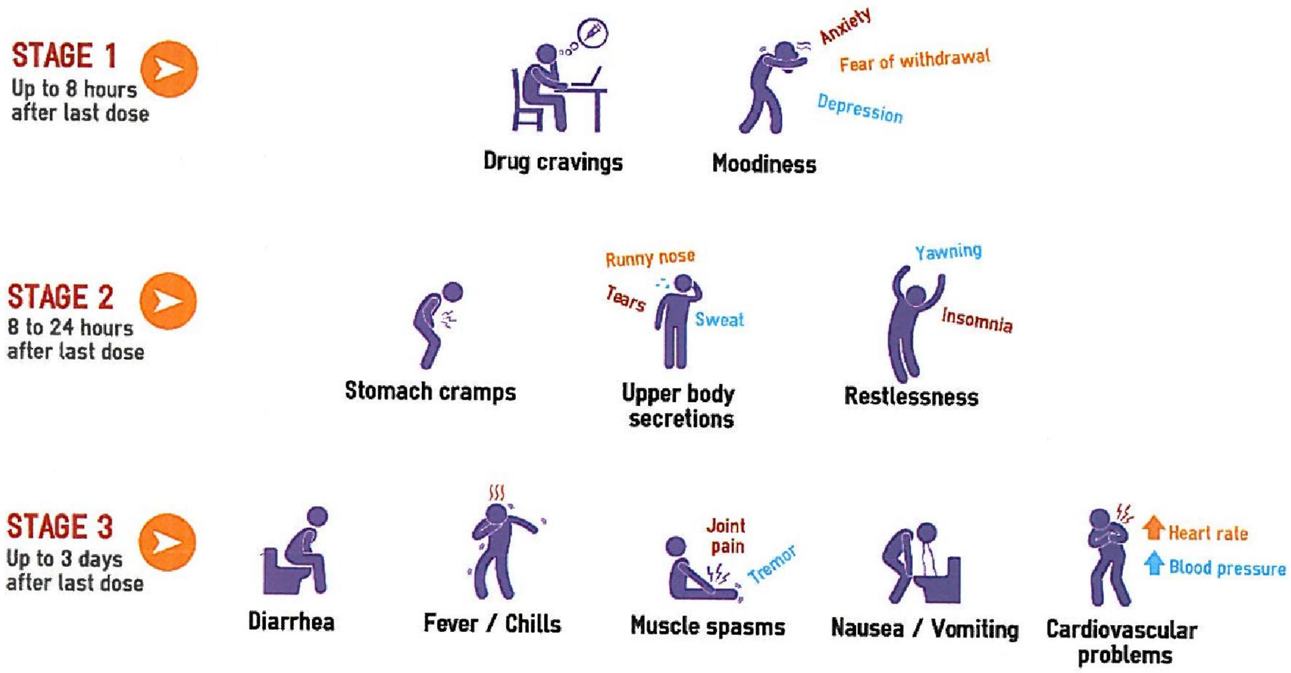
## Nalmefene (Revex®)

- **Nalmefene**, is a ***derivative*** of **Naltrexone** (***similar*** in both **structure** and **activity**) ***but*** is **available** ***only*** for **IV** ***administration***, ***but*** has a ***longer*** **half-life**, and ***no*** **dose-dependent liver toxicity**.
- It is ***used*** in the ***management*** of **alcohol dependence** and **opioid dependence**.

# Opiate Withdrawal Symptoms

- **Opioid use** *disorders* resulted in **51,000 deaths** in **2013**, up from **18,000 deaths** in **1990**.
- *Continuous* **administration** of **opioids** *leads to* **dependence**, when the **drug** is **stopped** *abruptly after* **dependence** occur, the **withdrawal symptoms** are *appear*.
- The **onset** & **duration** of **withdrawal symptoms** are *varies*, **depending on** the **opioid** *discontinued*.

## Heroin Withdrawal Timeline


STAGE 1
Up to 8 hours after last dose
Drug cravings
Moodiness
Anxiety
Fear of withdrawal
Depression
STAGE 2
8 to 24 hours after last dose
Stomach cramps
Runny nose
Tears
Sweat
Upper body secretions
Yawning
Insomnia
Restlessness
STAGE 3
Up to 3 days after last dose
Diarrhea
Fever / Chills
Joint pain
Tremor
Muscle spasms
Nausea / Vomiting
Heart rate
Blood pressure
Cardiovascular problems

## Opioid Detoxification

### 1) Methadone Maintenance Treatment (MMT)

- **Methadone maintenance** has been ***used*** to ***treat*** **opioid dependence** for ***more than*** **45 years**.
- ***Long-term*** use of **Methadone** as a ***substitute*** (***drug replacement therapy***) to the **opioid** on which the **patient** was ***dependent***.
- ***Dose*** of **Methadone** in **maintenance treatment** *range from* **80-120** mg orally per day.

### 2) Buprenorphine Maintenance Treatment (BMT)

- **Studies** have *shown* **Buprenorphine** to be a ***safer*** over **Methadone** in **opiate replacement therapy**, due to its ***partial*** **agonist** and **cause** ***mild*** **withdrawal symptoms** and ***little*** **sedation**, **respiratory depression** or **hypotension** ***even at*** **high doses**.
- ***Some*** formulations of **Buprenorphine** (Suboxone® - Zubsolv®) are ***combined with*** the **opiate antagonist Naloxone** to ***protect*** of the **pill**, form to ***prevent*** **people** from ***crushing*** the **sublingual tablets** and **injecting** ***them***.
- May 26, 2016, ***FDA approve*** **Probuphine® implant** to releases a steady six-month dose of **Buprenorphine**.

### 3) Levacetylmethadol or Levo-α-acetylmethadol (LAAM) (OrLAAM®)

- **LAAM** is a ***long-acting*** (thrice-weekly dosing) **derivative** of **Methadone**, is indicated as a ***second-line*** **treatment**, if patients ***fail*** to **respond** to drugs like **Methadone** or **Buprenorphine**.
- It may cause ***life-threatening*** **QT interval prolongation**.

### 4) Opioid Antagonist

- **Naltrexone** (***monthly injection***) is ***used for*** **relapse prevention** of **alcohol** and **opioid dependence**.

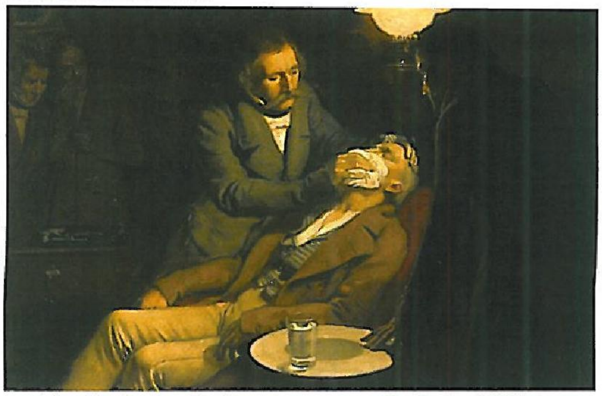
### 5) $\alpha_2$-adrenergic Agonist

- **Clonidine** and **Lofexidine** are used to ***control*** **sympathetic symptoms**.

# Anesthetics

## ➢ Overview:-

- **Anesthetic** (or **Anaesthetic**) is a **drug** ***that causes*** **anesthesia**.
- **Anesthesia** (or **Anaesthesia**) is an ***induced***, **temporary (reversible) state** with ***one*** or ***more*** of the ***following effects***;
  1) **Analgesia*** (***relief*** or ***prevention*** of **pain**).
  2) **Paralysis*** (**muscle relaxation**).
  3) **Amnesia*** (***loss*** of **memory**).
  4) **Inhibition** of **autonomic reflexes***.
  5) **Unconsciousness***.



The first use of ether as an anesthetic in 1846 by William Thomas Green Morton (American dentist)

- ***No single*** **anesthetic agent** currently available *when* **used alone** can achieve ***all 5*** *of these* **desired effects**.
- **Anesthetics** are categorized into *two classes*:
  - **General anesthetics**; which cause a ***reversible*** **loss of consciousness**.
  - **Local anesthetics**; which cause a ***reversible*** **loss** of **sensation** for a **limited region** of the **body** while ***maintaining*** **consciousness**.
- The **ideal anesthetic drug** ***should induce***; **1)** ***Rapid smooth*** **loss** of **consciousness**. **2)** ***Rapid*** **reversible** ***upon*** **discontinuation**. **3)** ***Possess*** **a wide margin** of **safety**.
- **Anesthetic drug** are **chosen** ***based on***; **1)** ***Type*** of **procedure**. **2) Patient** ***related factors*** (**organ function**, **medical conditions**, and **concurrent medications**).
- **Preanesthetic Medications**; is a **drugs** that is **given** ***before*** **anesthetic** to ***produce*** **optimal anesthesia** (i.e.; *to complete the missed effects from 5 desired effects*).

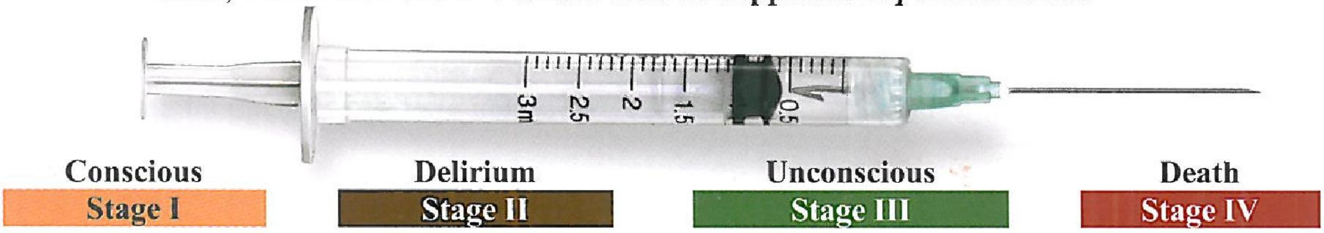
## ➢ Stages of Anesthesia [Depth of Anesthesia]:

- ***These stages*** were defined for the **original anesthetic Ether**, which *produces* a ***slow*** **onset** of **anesthesia**. With **modern anesthetics**, the **stages** ***merge because*** of the ***rapid onset*** of **stage III**.

1) **Stage I** (**Induction**); is the **period** *between* the ***initial*** **administration** of the **induction agents** and ***loss*** of **consciousness**, *during this stage*;
   - * **Patient conscious**.
   - * **Analgesia**.
2) **Stage II** (**Delirium/Excitement**); is the **period** *following* ***loss*** of **consciousness** and **excited** and **delirious activity**, *during this stage*;
   - * ***Irregular*** **respiration**.
   - * ***Irregular*** **heart rate**.
   - * ***Uncontrolled*** **movements**.
   - * **Vomiting**.
3) **Stage III** (**Surgical Anaesthesia**); is the ***ideal*** **stage** for **surgery**, *during this stage*;
   - * **Patient** is **unconscious**.
   - * ***Regular*** **respiration**.
   - * ***No*** **vomiting**.
   - * ***No*** **pain reflexes**.
   - * ***Normal*** **Blood pressure**.
   - * ***Normal*** **pupil size**.
   - * ***Slow*** **eye movements**.

   - *N.B.*; ***Careful*** **monitoring** is ***required*** *during this stage* to ***prevent*** **undesired progression** to **stage IV**.
4) **Stage IV** (**Medullary paralysis** or **overdose**); is the **stage** where ***too much*** **medication** has ***been*** **given** and the patient has ***severe*** **brain stem** or **medullary** ***depression***.
   - * **Respiratory** ***depression***.
   - * **Hypotension**.
   - * ***Very*** **weak pulse**.
   - * ***Death*** **may occur**.

   - *N.B.*; **Ventilation** and **circulation** ***must be*** **supported** to ***prevent*** **death**.



# Preanesthetic Medications

- **Premedications** ***facilitate*** **smooth induction** of **anesthesia** and ***lower required*** **anesthetic doses**.

## Anxiolytics (Sedatives)/Hypnotics

- **Benzodiazepines** (*still commonly used*); **Midazolam** (*short-acting*), **Lorazepam** (*intermediate-acting*) and **Diazepam** (*long-acting*) are ***commonly*** used. (**Barbiturates**, *not used much*).
  - ***Advantages***;
    - * Decrease anxiety.
    - * Providing amnesia.
    - * Induce postoperative sleep and relaxation.
    - * Reduce amount of anesthetics.
  - ***Disadvantages***; Depressant effect (cardiac and/or respiratory), **Barbiturates**; ***more*** **depressant**.

## Tranquilizers (Neuroleptics)

- Terms **sedatives** and **tranquilizers** are ***used*** **interchangeably**.
- ***Common*** **neuroleptics used** are **Chlorpromazine** (**CPZ**) and **Promethazine**.
  - ***Advantages***;
    - * Decrease postoperative nausea and vomiting.
    - * Decrease postoperative muscular pain caused by neuromuscular blockers.
  - ***Disadvantages***; Orthostatic hypotension.
- *N.B.*; **Neuroleptics** ***commonly*** used as a **preanesthetic** in **veterinary surgery**.

## Analgesics (Opioid/Non-Opioid)

- **Opioid Analgesics**; **Morphine**, **Meperidine** (or **Pethidine**) and **Fentanyl** are ***commonly*** **used**.
  - ***Advantages***;
    - * Provide sufficient analgesia during procedure and post operatively.
    - * Reduce amount of anesthetics.
  - ***Disadvantages***; Depressant effect (respiratory), nausea/vomiting and postoperative constipation.
- *N.B.*; **Droperidol** (*neuroleptic*) is **used** in ***combination*** with **Fentanyl** (*opioid*) in **neuroleptanalgesia**.
- **Non-opioids Analgesics** (**NSAIDs** and **Paracetamol**) *can be used* (***commonly*** **used postoperative**)

## Neuromuscular Blockers (NMBs)

- **Neuromuscular blockers**; *include* **Cisatracurium**, **Pancuronium**, **Rocuronium**, **Succinylcholine**, and **Vecuronium**, are described in *Autonomic chapter*.
  - ***Advantages***;
    - * Provide skeletal muscle relaxation.
    - * Abolish reflexes to facilitate tracheal intubation.
  - ***Disadvantages***; Histamine release (bronchospasm and hypotension), bradycardia and postoperative muscular pain (inhaled anesthetics enhance effect NMBs.).
- *N.B.*; **Sugammadex** (Bridion®) is approved by US FDA in December, 2015 for ***fast reversal*** of **neuromuscular blockade** by the **Rocuronium** or **Vecuronium** in **general anaesthesia**.

## Anticholinergics

- **Anticholinergics**; **Atropine**, **Hyoscine** (**Scopolamine**) & **Glycopyrronium** (**Glycopyrrolate**).
  - ***Advantages***;
    - * Reduce salivary, bronchial and GIT secretions.
    - * Protect the heart from bradycardia.
- *N.B.*; **Glycopyrrolate** little across to BBB (*little CNS effects*), ***in contrast to*** **Atropine** & **Hyoscine**.

## Others *(if needed)*

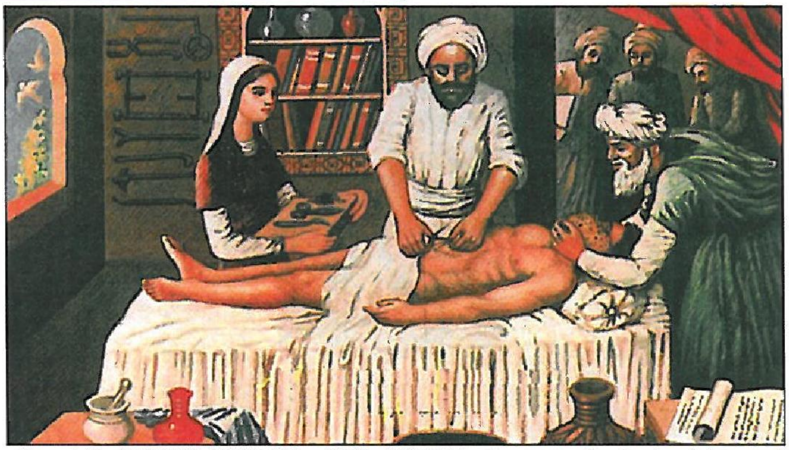
- **Antacids**; **$H_2$ blockers** (**Famotidine** and **Ranitidine**) to ***reduce*** **gastric acidity**.
- **Antiemetics**; **5-$HT_3$ blockers**; (such as, **Ondansetron**); to ***prevent*** **nausea** and **vomiting**.
- **Antihistamines**; **Diphenhydramine** to ***prevent*** **allergic reactions**.

# General Anesthetics

- **General anesthesia phases** (**stages**);
  1) **Induction**; is the **time** ***from*** **administration** of a **potent anesthetic** (**IV anaesthetics**) to ***development*** of **effective anesthesia**, depends on, ***fast effective*** **concentrations** of **anesthetic** ***reach the*** **brain**.
  2) **Maintenance**; ***provides*** **sustained anesthesia**, is ***commonly*** provided with **inhaled anesthetics**.
  3) **Recovery**; is the **time** ***from*** **discontinuation** of **anesthetic** ***until*** **consciousness**.
- **General anesthetics** are usually ***given by*** **inhalation** or by **intravenous injection**;
  - **Inhalation Anesthetics**; these are **gases** or **volatile liquids**, ***used primarily*** for ***maintenance*** of **anesthesia** ***after*** administration of an **IV anesthetics**.
    - *Advantages over intravenous agents*;
      - Depth of anesthesia can be changed rapidly by altering the inhaled concentration.
      - Not contribute to postoperative respiratory depression, due to rapid elimination.
  - **Intravenous Anesthetics**; *rapid loss* of **consciousness** and *induction* of **anesthesia**.
- **Balanced anesthesia**; includes the ***administration of*** **preanesthetic medications** *for* **sedation** and **analgesia**, **neuromuscular blockers**, or *both* **intravenous** and **inhaled anesthetics**.

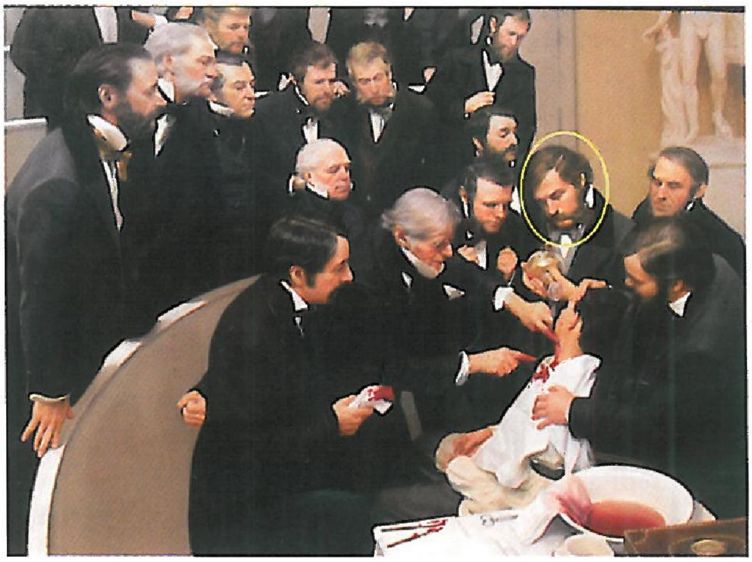
## Inhalation Anesthetics

Currently anesthesia gas machine is used



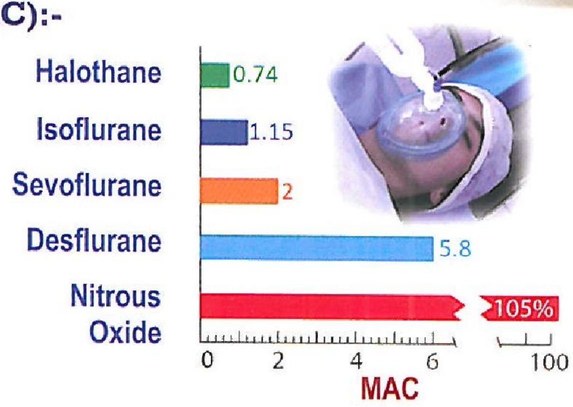
- Ibn al-Quff (1233-1286 AD م, 630 - 685 AH هـ) was an Arab physician and surgeon and author, he was used anesthesia by inhalation, by using anesthetic sponge.
- The sponge was soaked in a boiled solution made of water with cannabis (*from Arabic* hasheesh حشيش), opium (*from Arabic* afiun أفيون) and belladonna (*from Arabic* cit al huscin ست الحسن).
- The anesthetic sponge was placed it over the patient face, the liquid which is absorbed by the mucous membrane of nose and mouth.

- On October 16, 1846 at the operating theater of the Massachusetts General Hospital, (MGH), in Boston.
- Dr. John Collins Warren painlessly removed a tumor from the neck of a Mr. Edward Gilbert Abbott.
- Dentist William Morton was used Ether inhaler as a first inhalation anesthetic in surgery (*see photo*).
- This ranks as one of the most significant events in the history of Medicine.
- People around the world annually celebrate **World Anaesthesia Day** on October 16.



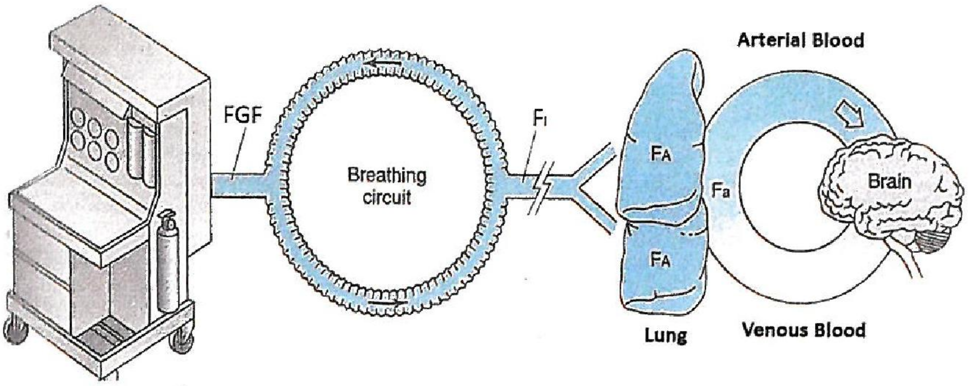
## ➢ Minimum Alveolar Concentration (MAC):-

- **MAC**; is the ***minimum*** **concentration** of **inhaled anesthetic** in the lung ***needed to*** **produces anesthesia** in **50%** of **patients.**
- MAC *used to* **measures** the **potency** of **inhaled anesthetics**, MAC is *small* for **potent** anesthetics such as **Halothane** and *large* for **less potent agents** such as **Nitrous oxide**.
- **Factors** that can ***increase*** **MAC**; hyperthermia, drugs that increase CNS catecholamines, and chronic ethanol abuse.



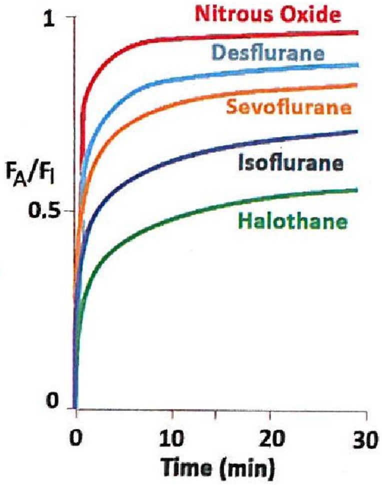
- **Factors** that can ***decrease*** **MAC**; increased age, hypothermia, pregnancy, sepsis, acute intoxication, concurrent IV anesthetics and $\alpha_2$-adrenergic receptor agonists (**Clonidine**).

## ➢ Uptake and Distribution of Inhalation Anesthetics:-

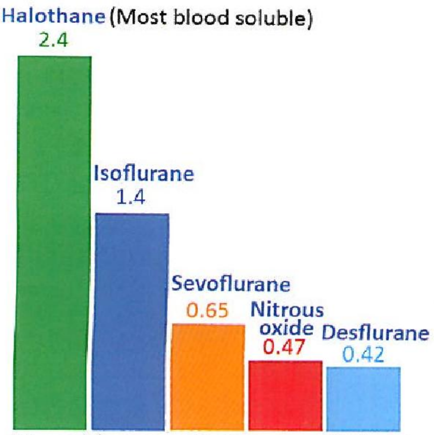


- **Factors raising the alveolar anesthetic concentration** (If no uptake by blood);
  - **Inspired Concentration** ($F_I$); is the concentration of an inhaled anesthetic in the inspired gas mixture; ↑ inspired anesthetic concentration ⇨ ↑ alveolar anesthetic concentration ⇨ ↑ rate of transfer into the blood ⇨ ↑ rate of induction of anesthesia.
  - **Alveolar Ventilation** ($V_{alveolar}$); is the volume of fresh gases entering the alveoli per minute; ↑ minute alveolar ventilation (i.e. ↑ rate and depth of ventilation) ⇨ ↑ alveolar concentration ($F_A$).
  - **Time constant**; is the time required for flow through a container to equal the capacity of the container. The time constant for the lungs is $FRC/V_{alveolar}$.
  - **Functional Residual Capacity (FRC)** is the volume of air present in the lungs at the end of passive expiration. ↑ FRC ⇨ ↓ washin of a new gas.
  - **$F_A/F_I$ Ratio**; ratio of alveolar agent to inhaled agent, is an important determinant of the speed of induction.
    - ↓ Blood anesthetic solubility ⇨ ↑ $F_A/F_I$.
    - ↓ Cardiac output ⇨ ↑ $F_A/F_I$
    - ↑ Minute ventilation ⇨ ↑ $F_A/F_I$.

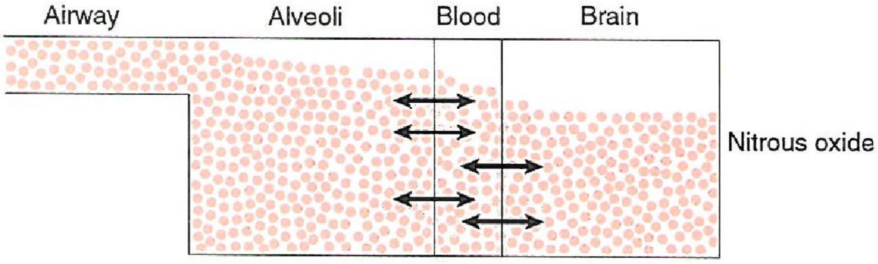
$F_A/F_I$ fastest for the least soluble agents (**Nitrous oxide**)

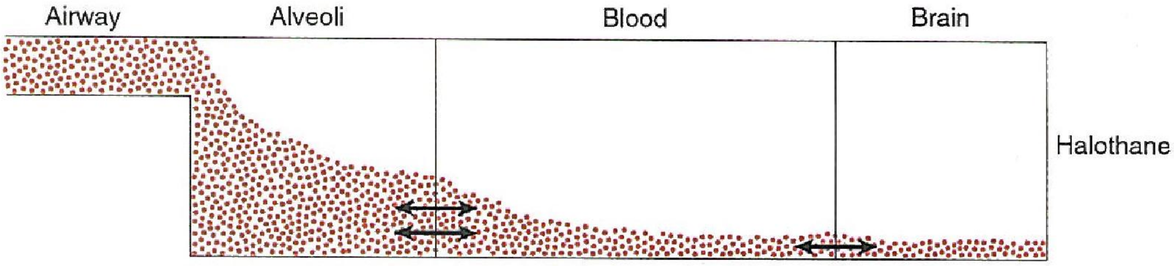


- **Factors Controlling Anesthetic Uptake**;
  - **Blood Solubility**; is the transfer of an anesthetic from the lungs to the arterial blood to the brain and other tissues.
    - This is determined by; **blood/gas partition coefficient** (**PC**); the ratio of the concentration of anesthetic in the blood to the concentration of anesthetic in the gas that is in contact with that blood when the partial pressure in both is equal.
    - ↓ Blood gas PC ⇨ rapid onset of induction and recovery (**Nitrous oxide**).
    - ↑ Blood gas PC ⇨ slow onset of induction and recovery (**Halothane**).



Blood/gas partition coefficient





  - **Cardiac Output**; ↑ pulmonary blood flow (i.e., ↑ cardiac output) ⇨ ↑ anesthetic remove from the alveoli (↑ uptake of anesthetic) to peripheral tissues (not the site of action) ⇨ ↓ rate of rise in alveolar concentration of gas ⇨ ↓ rate of induction of anesthesia.
    - ↓ CO (shock) ⇨ ↑ rate of rise of the alveolar concentration of gas (*So*, IV anesthetics more suitable and safe).
  - **Alveolar-venous Partial Pressure Difference**; The anesthetic partial pressure difference between alveolar (arterial) and mixed venous blood is dependent mainly on uptake of the anesthetic by the tissues.
    - ↑ Difference in anesthetic concentration between alveolar and mixed venous blood, ⇨ ↑ uptake ⇨ ↓ induction.
    - At equilibrium, the venous partial pressure = arterial partial pressure = alveolar partial pressure (uptake = 0).
- **Washout** (**Recovery**); When an inhalation anesthetic is discontinued, the body drives the anesthetic back into the alveolar space.
- ***Characteristics of inhalation anesthetics***;

| Anesthetic | MAC (%) | Blood/Gas | Oil/Gas | Brain/Blood | Muscle/Blood | Fat/Blood |
|---|---|---|---|---|---|---|
| Nitrous Oxide | 105 | 0.47 | 1.4 | 1.1 | 1.2 | 2.3 |
| Halothane | 0.74 | 2.4 | 224 | 2.9 | 3.5 | 60 |
| Isoflurane | 1.15 | 1.4 | 97 | 2.6 | 4.0 | 45 |
| Sevoflurane | 2 | 0.65 | 42 | 1.7 | 3.1 | 48 |
| Desflurane | 5.8 | 0.42 | 18.7 | 1.3 | 2.0 | 27 |

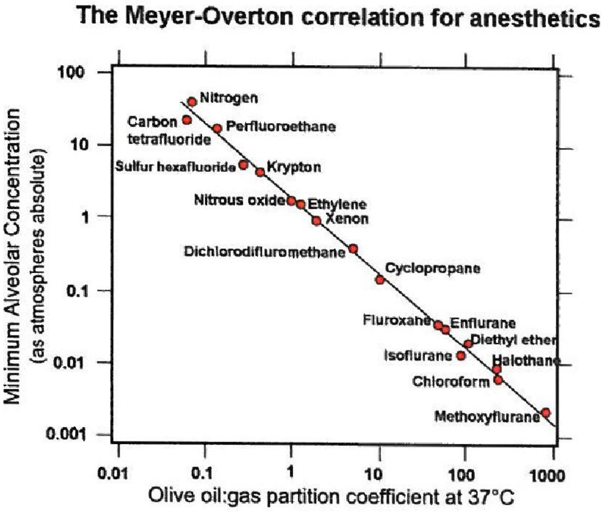
## ➢ Mechanism of Action:-

- **General anesthetics** have been in clinical use for ***more than*** **160 years,** ***but*** their **mechanism of action *remains* unknown.**
- ***Theories of the possible mechanisms***;

  A) **Lipid Theory**; *first proposed in 1847*, They suggested that **general anaesthetics** may act by ***dissolving*** in the **fatty fraction** of **brain cells** and ***removing*** **fatty constituents from them,** thus ***changing*** **activity** of **brain cells** and ***inducing*** **anaesthesia** (In 1899 Hans Horst Meyer published the first experimental evidence of the fact that anaesthetic potency is related to lipid solubility; The Meyer-Overton correlation).

  B) **Ion Channels**;

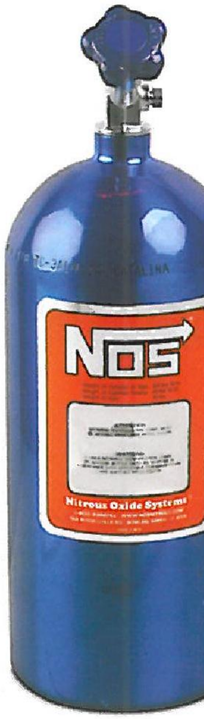
  1) Potentiate $GABA_A$ receptors sensitivity to GABA.
  2) Inhibition of NMDA receptors.
  3) Increase activity of the inhibitory glycine receptors.


The Meyer-Overton correlation for anesthetics

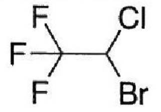
## ➢ Inhalation Anesthetics:-

### Nitrous Oxide ($N_2O$)

- **Nitrous oxide** [NYE-truss OX-ide], is an **oxide of nitrogen,** ***commonly known as*** **laughing gas, nitrous, nitro** or **NOS,** it was discovered in 1793.
- ***At room temperature***; it is a **colourless volatile gas,** ***non*-flammable gas,** with a *slightly sweet* **odour** and **taste.**
- It is a ***non*-irritating *potent*** **analgesic *but*** a ***weak*** **general anesthetic,** if **used *alone*** *cannot* **produce surgical anesthesia,** ***but*** it is ***commonly combined*** with *other* ***more*** **potent anesthetic.**
- It is ***used*** in **surgery** and **dentistry** for its **anaesthetic** and **analgesic effects.** It is known as **"laughing gas"** ***due to*** the **euphoric effects** of inhaling.
- **Nitrous oxide** is ***poorly*** **soluble** in **blood** and **other tissues,** allowing it to ***move very*** **rapidly in** (***induction***) and **out** (***recovery***) of the ***body***.
- ***Concentrations***; in ***general anesthesia***, **30 %** to **70 %** in ***combination*** with **oxygen.**
- ***Safety***; **Nitrous oxide *does not depress*** **respiration** and ***does not produce*** **muscle relaxation,** ***little*** or ***no effect*** on **CVS** or **cerebral blood flow,** ***last*** **hepatotoxic *effect*.**
- ***Side effects***; **Hallucination, *Postoperative*** **nausea** and **vomiting.**
- ***Prolonged*** **exposure** may cause **megaloblastic anemia** (due to decrease methionine synthase activity).

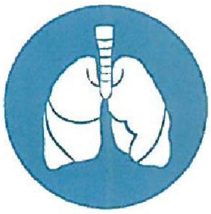


## **Halothane** (Fluothane®)



- **Halothane** [HAL-oh-thane] is ***halogenated hydrocarbon***.
- *At room temperature*; it is **colourless volatile liquid**, *non*-**flammable** and *pleasant*-**smelling**, *but* **light sensitive** (*packaged* in **dark-coloured bottles**).
- *It is produce*; *rapid* **induction**, *quick* **recovery**, *not adequate* **analgesia** (usually co-administered with **Nitrous oxide**, **opioids**, or **local anesthetics**) and *not sufficient* **muscle relaxation** (**neuromuscular backers** *may be required*, **dose** *must be adjusted*, due to **Halothane** *markedly augments* the **non-depolarizing neuromuscular blocking effects**).
- *Metabolism*; by **oxidation** to **tissue-toxic hydrocarbons** (e.g. **Trifluoroethanol**) and **Bromide ion**.
- *Uses*; *induction* and *maintenance* of **general anesthesia**.

- *Depress* **heart contractility**.
- *Induces* **vasodilation**.
- *Decrease* **cardiac output**, **arterial pressure** and **heart rate**.
- *Severe* **hypotension & circulatory** *failure may occur with* **over-dosage**.
- **Cardiac arrhythmias (hyperkalemia)** *may occur during* **induction**.



- *Non*-**irritate** to the **respiratory tract**.
- *Depress* **pharyngeal** and **laryngeal** *reflexes*.
- *Dilates* the **bronchioles**.
- *Decrease* **salivation** and **bronchial** *secretions*.
- **Halothane** and **Sevoflurane** *agents of choice* in *patients with* **airway problems** (*not have* **pungent odour** to *stimulate* **respiratory reflexes**).

*** Hepatotoxicity (Halothane Hepatitis) ***

- *Transient*, *slight* **abnormalities** in the *results* of **liver function tests** have been *observed* after a *single* **administration**.
- **Liver damage**, *ranging* from *mild* **hepatitis** to *massive* **hepatic necrosis** (**hepatitis** incidence, *approximately* 1 in 10,000 and **massive hepatic necrosis** is about 1 in 95,000).
- **Liver damage** is *more likely* to develop following *repeated* **administration** of **Halothane** (at **intervals** of *less than* **6 weeks**).
- **Halothane** *contraindicated* in patients with jaundice or **acute liver damage**.

*** Malignant Hyperthermia ***

- Is a *rare* **life-threatening** genetic disorder of skeletal muscle, that usually occurs in ***susceptible patients***, exposure to halogenated hydrocarbon anesthetics (e.g. **Halothane**) and depolarizing neuromuscular blocker **succinylcholine** (*rapid* ↑ **muscle metabolism**).
- ***Characterized by:***
  - Very high temperature and unexplained tachycardia.
  - Muscle rigidity and intensive pain (due to increase muscle contraction and abnormal increase of $Ca^{2+}$ from sarcoplasmic reticulum).
  - Metabolic acidosis (the body produces excessive quantities of acid or kidneys are not removing enough acid from the body).
- ***Treatment by:***
  - Cooling patient.
  - **Dantrolene** [DAN-tro-lean] ***(Direct skeletal muscle relaxant)*** ⇨ Prevent release of $Ca^{2+}$ from sarcoplasmic reticulum.

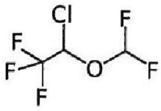
- **Halogenated anesthetics** (e.g. **Halothane**) are *potent* **uterine muscle** *relaxants*.
- *Due to* **side effects**; **Halothane** has been *replaced* in *most* **countries** by **newer agents** such as **Sevoflurane**, **Isoflurane** and **Desflurane**.

## ➢ Brief Comparison between Nitrous Oxide and Halothane*:-

| **Nitrous Oxide ($N_2O$)** | **Halothane** (Fluothane®) |
|---|---|
| - Colorless volatile gas. | - Colorless volatile liquid. |
| - Low blood/gas partition coefficient = 0.47<br>☞ Rapid onset of action and recovery. | - High blood/gas partition coefficient = 2.4<br>☞ Slow onset of action and recovery. |
| - Weak anesthetic (MAC = 105%). | - Potent anesthetic (MAC = 0.74%). |
| - Adequate analgesic activity. | - Not adequate analgesic activity. |
| - Little or no side effects on CVS. | - Side effects on CVS. |
| - Little or no hepatotoxic effect. | - Hepatotoxic effect. |
| - Good choice in patients with liver injury. | - Good choice in patients with airway problems. |

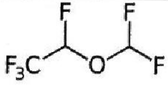
## ➢ Modern Inhalation Anesthetics:-

### Isoflurane (Forane®)



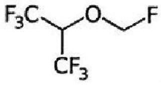
- **Isoflurane** [eye-so-FLOOR-ane], is a ***halogenated*** **ether**.
- **Isoflurane** is a ***structural isomer*** of **Enflurane** (Ethrane®), **Enflurane *no* longer use** *due to* ***depression*** **of myocardial contractility**, ***higher*** **metabolism** (***high*** **toxic metabolites**, ***potentially*** **nephrotoxic**) and ***lower*** **seizures threshold**.
- ***Little*** **metabolism** (***less*** **toxic metabolites**), ***no*** or ***little*** **hepatotoxicity**.
- ***N.B.***; **Hepatic metabolism rank** for **inhaled anesthetics** is; **Halothane** > **Enflurane** > **Sevoflurane** > **Isoflurane** > **Desflurane** > **Nitrous oxide**.
- **Cardiac arrhythmias** or ***dose-dependent*** **hypotension** ***may occur*** (*Other* ***newer*** **inhaled anesthetics** **Desflurane** and **Sevoflurane** are considerably ***less*** **arrhythmogenic**).
- It has a **pungent odour** and ***stimulates*** **respiratory reflexes** (breath holding, salivation, coughing and laryngospasm or bronchospasm), so ***not*** **used** in for **inhalation induction**.
- ***Used*** for ***maintenance*** of **general anesthesia**.
- ***Concern***; Use of **Isoflurane** and **Ketamine** in ***together*** in **infants** or **young children**, may ***increase*** **risk** of **neurodegeneration**.
- ***Now***; **Isoflurane** is ***being*** **replaced** ***with*** **Sevoflurane** and **Desflurane**.

### Desflurane (Suprane®)



- **Desflurane** [DES-floor-ane] is a ***fluorinated*** **methyl ethyl ether**.
- It is ***very*** **rapid onset** and **recovery** due to ***low*** **blood solubility**.
- ***Like*** **Isoflurane**, it has a **pungent odour**, ***used*** for ***maintenance*** of **general anesthesia**, ***but*** due to ***high*** **cost** may ***precludes*** its use.
- ***Metabolism***; is ***minimal*** and **tissue toxicity** is ***rare***.

### Sevoflurane (Sevorane®)



- **Sevoflurane** [see-voe-FLOOR-ane] is a **fluoromethyl hexafluoroisopropyl ether**.
- It has ***low*** **pungency**, ***used*** for ***induction*** and ***maintenance*** of **general anesthesia** in **adult** ***and*** **paediatric**.
- It has a ***rapid*** **onset** and **recovery** due to ***low*** **blood solubility**.
- ***Metabolism*** of **Sevoflurane** may ***generate*** **toxic metabolites** that are ***potentially*** **nephrotoxic**.
- ***N.B.***;
  - **Isoflurane**, **Desflurane** and **Sevoflurane** are a ***trigger*** of **malignant hyperthermia**.
  - **Mutagenicity**, **teratogenicity**, **reproductive effects** and **carcinogenicity** are a **chronic toxicity** for **inhalation anesthetics**, ***increase*** in **operating room personnel** who were exposed to trace concentrations of anesthetic agents.
  - **Methoxyflurane** is ***another*** **halogenated anesthetic** has ***not been*** **hepatotoxicity** *reported* after administration, *However*, **fluoride** ***release*** *from* **prolonged use** of **Methoxyflurane** has caused ***renal insufficiency***.

# Intravenous Anesthetics

- They are ***widely* used** to **facilitate** ***rapid* induction** of **anesthesia**.
- ***Once*** the **drug** has ***injected*** and ***reach*** to **CNS**, it ***exerts*** its **effects**.
- ***Like*** **inhalation anesthetics**, the ***exact*** **mechanism of action** is ***unknown***.

## Barbiturates

### **Thiopental** (Pentothal®) | **Methohexital** (Brevital®)

- **Thiopental** [thye-oh-PEN-tal], the ***first*** **intravenous anesthetic**, was synthesized in 1934.
- **Thiopental** and **Methohexital** [meth-oh-HEX-uh-tall] are an ***ultra-short-acting*** **barbiturates**.
- ***This agents*** have been ***largely replaced*** as **induction anesthetics** by **Propofol.**
- It is a ***potent*** **anesthetic** **but** a ***weak*** **analgesic**.
- **Thiopental** ***induce*** **anesthesia** ***within*** **30-60 seconds** ***after*** **IV injection**.
- ***All*** **barbiturates** are ***potent*** **cardiac** and **respiratory depressant**, *These agents* have been ***largely replaced*** as **induction anesthetics** by **Propofol**.
- *General barbiturate pharmacology are discussed in page no. 281.*

## Benzodiazepines

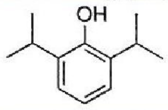
### **Midazolam** (Dormicum®) | **Lorazepam** (Ativan®)

### **Diazepam** (Valium®)

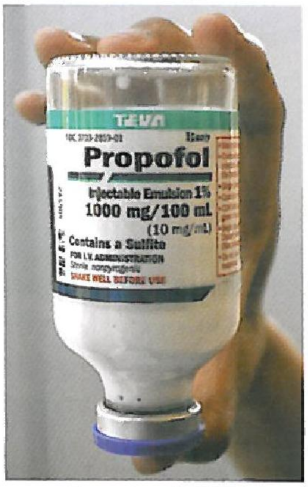
- **Benzodiazepines** (*still commonly used*); **Midazolam** (*short*), **Lorazepam** (*intermediate*) and **Diazepam** (*long*) are ***commonly*** used in **preanesthetic medications** with **anesthetics**.
- Their ***most*** **desired effects** are **anxiolytic** and **providing amnesia**.
- ***All*** **benzodiazepines** are ***minimal*** **cardiac** and **respiratory depressant**.
- *General benzodiazepines pharmacology are discussed in page no. 277.*

## Intravenous Anesthetics

### **Propofol** (Diprivan®)



- **Propofol** [PRO-puh-fol] is a ***short-acting*** **IV anesthetic** (***potent*** **anesthetic** but a ***weak*** **analgesic**) ***used for induction*** and ***maintenance*** of **anesthesia**. It is ***widely*** **used** and has ***replaced*** **Thiopental** as the ***first choice*** for ***induction*** of **anesthesia**.



- ***Formulation***;
  - **Propofol** is a 2,6-diisopropylphenol (alkyl phenol).
  - ***Poor*** **solubility** in **water**, it is formulated as an **emulsion** (10% soybean oil, 2.25% glycerol and 1.2% lecithin{egg phospholipid}), it has been ***referred to*** as **milk of amnesia** ***because*** of the **milk-like appearance** (it is ***contraindicated*** in patients with allergies to **eggs** or **soy products**)
  - ***Not used*** after **8 hours** of **vial opening** (*bacterial growth*).
- ***Pharmacokinetics***;
  - ***Onset***: **30-40 seconds** ***after administration***.
  - ***Duration***; **5-10 minutes**.
  - ***Metabolism***; ***Rapidly*** **metabolized** in the **liver**.
  - ***Excretion***; ***inactive*** **water soluble metabolites** are **excreted** ***renally***.
- ***Mechanism of Action***; ***poorly understood***, is thought to ***potentiate*** **GABA$_A$ receptors** to **GABA**.
- **Propofol** ***produces***;
  - ***Decrease*** **blood pressure** (*without depressing the myocardium*).
  - ***Minimal*** **respiratory depressant**.
- ***Sub-anesthetic*** **doses** of **Propofol** can be ***used*** to ***treat*** **postoperative nausea** and **vomiting**.
- The **respiratory depressant** of **Propofol** are ***increased if*** given with ***other*** **respiratory depressants** (**benzodiazepines**), Michael Jackson was died of acute **Propofol** & **benzodiazepine** intoxication at home.
- **Fospropofol** (Lusedra®) is a ***water-soluble prodrug*** of **Propofol**, ***approved*** in **2008** as a **sedating agent** for ***use*** during **Monitored Anesthesia Care** (**MAC**).

## Etomidate (Amidate®)

- **Etomidate** [ee-TOM-uh-date] is a ***short-acting*** **IV anesthetic**, ***used for induction*** of **anesthesia**.
- **Etomidate** ***not*** has **analgesic effects**.
- ***Formulation***; it is ***poorly*** **soluble** in **water** and is ***formulated in*** a **propylene glycol** ***solution***.
- ***Pharmacokinetics***;
    - ***Onset***; **30-60 seconds** ***after administration***.
    - ***Duration***; ***depends*** on **redistribution** to inactive tissue sites.
    - ***Metabolism***; *Primarily* by **ester hydrolysis**.
    - ***Excretion***; ***Inactive*** **metabolites** are excreted in **urine** (78%) and **bile** (22%).
- ***Mechanism of Action***; ***poorly understood***, is thought to ***potentiate*** **GABA$_A$ receptors** to **GABA**.
- It has ***little*** or ***no*** **effect** on the **heart** and **circulation**, it is **used** ***especially*** in **patients** ***with*** **cardiovascular dysfunction**.
- ***Side effects***; ***decrease*** **plasma cortisol** and **aldosterone levels** (*increased with prolonged infusion*).
- ***Combination*** of **Etomidate** with **opioids** and/or **benzodiazepines**, may exacerbate **Etomidate**-***related*** **adrenal insufficiency**.

## Ketamine (Ketalar®)

Photos from "Mafia"Arabic movie

- **Ketamine** [KET-uh-meen] is a ***short-acting***, ***non***-**barbiturate anesthetic**.
- It ***induces*** **dissociative anesthesia** (**trance-like state**); **analgesia-amnesia state** in which the **patient's eyes** ***remain*** **open**, but is ***dissociated from*** the **environment**, is **immobile** and ***does not respond*** to **pain**.
    - ***Routes of Administration***; **IV**, **IM**, **oral**, & **topical routes**.
    - ***Onset***; **IV**; ***within*** a **minute**, **IM**; 5-15 min, **Oral**; 30 min.
    - ***Duration***; ***More*** **prolonged** (*depend on elimination*).
    - ***Metabolism***; In the **liver** by **CYP450 system**.
    - ***Excretion***; In **urine**.
- ***Mechanism of Action***; *Acts* **primarily** as an **NMDA** ***antagonist***.
- It ***has*** **effect** on the **heart** and **circulation** (***increase*** **blood pressure** and **CO**).
- It is ***not*** produce **respiratory depression**, and ***may*** cause **bronchodilation**, It ***increase*** **cerebrospinal fluid** ***pressure***.
- It is ***beneficial*** in **patients** ***with*** **hypovolemic** or **cardiogenic shock** and **asthmatic**.
- ***Side effects***; **Psychic disturbances** (**unpleasant dreams**, **delirium** and **hallucinations**).
- **Ketamine** may be *used* **illicitly**, **"ecstasy drug"** it causes a ***dream-like*** **state** and **hallucinations** *similar to* **Phencyclidine** (**PCP**).

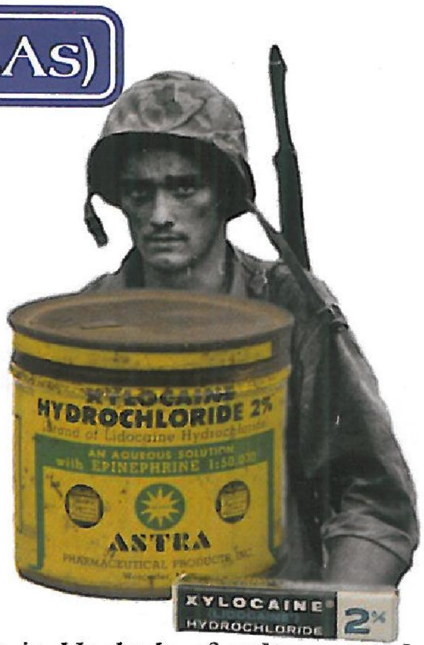
## Dexmedetomidine (Precedex®)

- **Dexmedetomidine** [dex-med-eh-TOM-uh-deen] is an **$\alpha_2$ receptor** ***agonist***.
- It has **sedative**, **analgesic**, **sympatholytic** and **anxiolytic effects**.
- It is ***not*** produce **respiratory depression**, It has ***moderate decrease*** in **blood pressure** & **heart rate**.

## Droperidol / Fentanyl (Innovar®)

- **Droperidol** (antipsychotic) in ***combination*** with **Fentanyl** (opioid) usually provide **amnesia** and **analgesia**, and has been ***used*** to ***produce*** **neuroleptanalgesia** and **neuroleptanesthesia**.
- ***Neuroleptanalgesia***; an **anesthetic** ***process*** that involves ***combining*** a **neuroleptic** (major tranquilizer or antipsychotic) and the potent **opioid analgesic** to produce ***state of*** **sedated analgesia**.
- ***Side effects***; **Hypotension**, **QT interval** ***prolongation***, and **extrapyramidal syndrome**.

# Local Anesthetics (LAs)


XYLOCAINE
HYDROCHLORIDE 2%
Brand of Lidocaine Hydrochloride
AN AQUEOUS SOLUTION with EPINEPHRINE 1:50,000
ASTRA
PHARMACEUTICAL PRODUCTS, INC.
XYLOCAINE HYDROCHLORIDE 2%

- **Local Anesthetic** is a **drug** that ***block*** **sensations** of **pain** from a ***specific*** **area** of the **body**.
- **Cocaine** is the ***first only*** **naturally anesthetic discovered** and ***used*** as a **local anesthetic** in **1884**.
- **Benzocaine** is the ***first*** **synthetic** derivative of **Cocaine**, was developed in **1890**.
- **Lidocaine** is the ***most widely used*** **local anesthetic** during **World War II** in **1943**.
- **Lidocaine** had a ***more*** **favourable duration of action** ***than*** **Procaine**, and ***less*** **systemic toxicity** ***than*** **Tetracaine**.
- ***To this day***, **Lidocaine** ***remains*** **one** of the **most** ***widely*** **used anesthetics**.

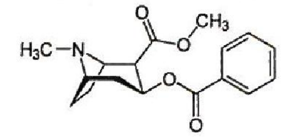
## ➢ Mechanism of Action:-

- The ***primary*** **mechanism** of **action** of **local anesthetics** is ***blockade*** of **voltage-gated sodium channels**, ***prevents*** the **rapid influx** of **$Na^+$ ions**, which are ***essential for*** **nerve action potential**.
- ***All*** **nerve fibers** are **sensitive** to **local anesthetics**, ***but*** due to they are ***different*** in **diameter** and **myelination**, **fibers** have ***different*** **sensitivities** to **local anesthetic**;
  - Type B fibers (sympathetic tone) are the most sensitive followed by Type C (Pain), Type A delta (temperature), Type A gamma (proprioception), Type A beta (sensory touch and pressure) and Type A alpha (motor).

## ➢ Classifications (*common agents and uses*):-

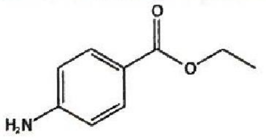
### Esters

#### Cocaine



- **Cocaine** is the ***first*** **local anesthetic** used in **1884**.
- **Cocaine** or **coke** is a ***strong*** **stimulant** ***mostly used*** **illegal drug** ***globally***.
- **Cocaine** ***inhibits*** **reuptake** of **serotonin, norepinephrine** and **dopamine**.
- **Cocaine** is the ***second*** **most popular illegal drug** in **Europe**.
- ***Current*** **clinical use** of **Cocaine** is ***largely*** **restricted** to **topical anesthesia** for **ear, nose** and **throat** procedures, due to ***intense vasoconstriction*** can serve to ***reduce*** **bleeding**.
- **Cocaine** has since been ***largely replaced*** in **medicine** by ***synthetic*** **local anesthetics**.

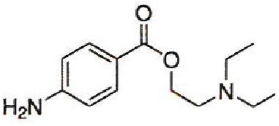
#### Benzocaine



- **Benzocaine** [BEN-zoe-kane] is the ***first*** **synthetic** derivative of **Cocaine**, was developed in **1890**.
- It is ***found*** in many **OTC anesthetic products** ***used mainly*** for **oral ulcers**.
- The **topical use** of ***higher concentration*** of **Benzocaine** may ***cause*** **Methemoglobinemia** (a ***life-threatening*** condition in ***which*** the **amount** of **oxygen** ***carried by*** the **blood** is ***greatly reduced***), this ***side effect*** is **most common** in **children** ***under*** **2** **years**.

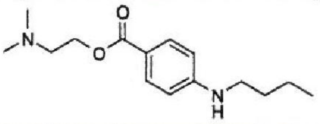
(*Do not use* Benzocaine local preparations in children under 2 years)

#### Procaine (Novocain®)



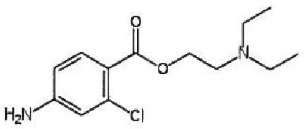
- **Procaine** [PRO-kane] was ***first synthesized*** in **1905**.
- ***To this day***, **Procaine** is ***used less frequently***.
- **Procaine** and ***many*** **other local anesthetics** are ***used mainly*** in ***combination*** with **Epinephrine** (vasoconstrictor), ***to***;
  1) Reduce bleeding.
  2) Increases duration and quality of anesthesia (decrease absorption).
  3) Decrease amount of drug from reaching systemic circulation.

### Tetracaine (Pontocaine®)



- **Tetracaine** [TET-truh-cane] was ***first synthesized*** in **1930**.
- It is ***mainly used topically*** in **ophthalmology** (topical local anesthetic for the eyes).

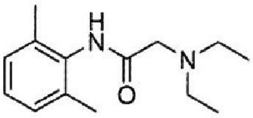
### Chloroprocaine (Nesacaine®)

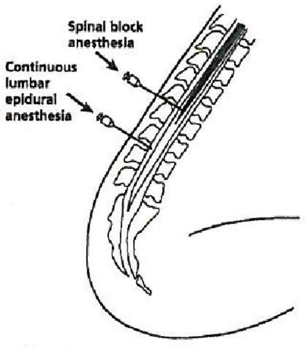


- **Chloroprocaine** [klor-oh-PROE-kane] is ***rapidly*** **metabolized** and ***placental*** **transfer** is ***limited***, so, it is ***used*** as **obstetric anesthesia**, for **epidural anesthesia**. **Epidural anesthesia** is the ***most*** **popular** method of **pain *relief* during labor**.

## Amides

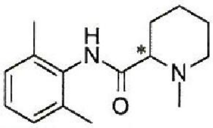
### Lidocaine (Xylocaine®) (Lignocaine®)





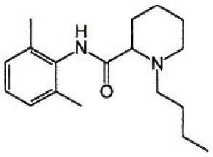
- **Lidocaine** [LYE-doe-kane] ***used*** **systemic** as an **antiarrhythmic drug** (Class Ib; sodium channel blockers) and **locally** as **local anesthetic**.
- **Lidocaine** is **one** of the ***most important*** **medications** ***needed*** in a **basic health care system**.
- ***Like* Chloroprocaine**, ***sometimes used*** for **epidural anesthesia**.
- ***Like* Tetracaine**, ***can*** be ***used topically*** in **ophthalmology**.
- ***Inhaled* Lidocaine** can be ***used*** as an **antitussive** (*reduce cough reflex*).
- **Lidocaine** is ***available*** in ***multiple*** **formulations** and ***most widely*** **used**.

### Mepivacaine (Mepecaine®)



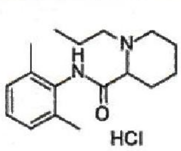
- **Mepivacaine** [muh-PIV-uh-kane] is a **local anesthetic** with ***rapid*** **onset** and ***medium*** **duration of action**.
- It ***may used*** for **epidural anesthesia** (poor choice).

### Bupivacaine (Marcaine®)



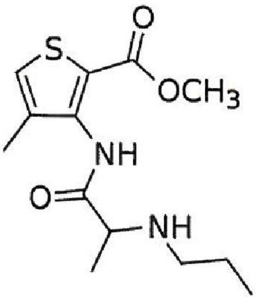
- **Bupivacaine** [byoo-PIV-uh-kane] is a **local anesthetic *used*** for **epidural anesthesia**, ***but*** it has ***markedly*** **cardiotoxic**.
- **Levobupivacaine** (Chirocaine®) is the ***S-enantiomer*** of **Bupivacaine**, *with **less*** **cardiotoxic**, ***less*** **potent** and ***longer*** **duration** than the racemic mixture.

### Ropivacaine (Naropin®)



- **Ropivacaine** [roe-PIV-uh-kane] was developed after **Bupivacaine**, was *with **less*** **cardiotoxic**.
- It is also a ***popular choice*** for **nerve block anaesthesia** and **epidural anesthesia**.

### Articaine (Septocaine®)



- **Articaine** [AR-ti-kane] it was ***approved*** in **USA** as a **dental anesthetic** in 2000.
- It is ***generally*** considered to be ***more*** **effective** and possibly ***safer*** than **Lidocaine**.
- It also available in a ***combination*** with **Epinephrine**.
- **Articaine** is the ***best choice*** of **local anesthetic** in ***modern*** **dentistry**.
- ***Characteristics over than other*** **local anesthetics**; ***low*** **lipid solubility**, ***high*** **plasma protein binding**, ***fast*** **metabolization**, ***fast*** **elimination** and ***low*** **blood level**.

## Prilocaine

- **Prilocaine** [PRIL-oh-kane] also ***combined with*** **Lidocaine** as a ***topical*** **preparation** for **dermal anesthesia**.
- EMLA® (**E**utectic **M**ixture of **L**ocal **A**nesthetics); **Lidocaine** and **Prilocaine** are **solid bases**, when mixed in equal quantities, they form a **eutectic mixture**, that is the **melting point** of the **mixture** is ***lower than*** the **melting points** of the **individual components**.

### ➢ Pharmacokinetics:-

- *Absorption*;
  - ***Factors affecting local anesthetics absorption***;
    - **Dosage** (↑ dose ⇨ ↑ absorption).
    - **Site of injection** (↑ local tissue blood flow ⇨ ↑ absorption).
    - **Protein binding** (↑ protein binding ⇨ ↑ duration of action).
    - **Use of a vasoconstrictor** e.g. **Epinephrine** (↓ absorption).
    - **Physicochemical properties** (↑ lipid solubility ⇨ ↑ potency ⇨ ↑ action).
  - ***Properties of some ester and amide local anesthetics***;

| | Potency (Procaine = 1) | Duration of Action |
|---|---|---|
| Esters | | |
| Cocaine | 2 | Medium |
| Procaine | 1 | Short |
| Tetracaine | 16 | Long |
| Amides | | |
| Lidocaine | 4 | Medium |
| Mepivacaine | 2 | Medium |
| Bupivacaine | 16 | Long |
| Ropivacaine | 16 | Long |
| Articaine | 1.9 | Medium |

- *Distribution*;
  - **Localized**; **distribution *within*** the **area** *which the* **drug** is ***applied***, ↓ risk of toxicity.
  - **Systemic**, ***high*** **drug concentration** ⇨ ↑ **peak blood levels** ⇨ ↑ ***risk*** for **potential systemic toxicity** of the **local anesthetics**.
- *Metabolism*;
  - **Amides**; are metabolized in the **liver**.
  - **Esters**; are metabolized in **plasma** (by; **pseudocholinesterase enzyme**).
- *Excretion*; in the **urine**.

### ➢ Toxicity:-

- *Systemic Toxicity*;
  - **CNS toxicity**;
    - *Low toxicity*;
      - Circumoral and/or tongue numbness
      - Lightheadedness
      - Visual and auditory disturbances
      - Metallic taste
      - Dizziness
      - Drowsiness
    - *High toxicity*;
      - Muscle twitching
      - Unconsciousness
      - Respiratory depression and arrest
      - Convulsions
      - Coma
      - CV depression and collapse
  - **Cardiotoxicity**; Chest pain, palpitations, diaphoresis, hypotension and syncope.
  - **Hematologic toxicity**; **Methemoglobinemia** (cyanosis), frequently with **Benzocaine** (**Lidocaine** and **Prilocaine** have also been implicated).
  - **Allergic toxicity**; rash, urticaria & anaphylaxis (very rare), amino-esters such as **Procaine** is a derivative of the allergen ***para-aminobenzoic-acid*** (**PABA**).
- *Localized Toxicity*; neurotoxicity (nerve injury) and transient neurologic symptoms; TNS (rare spinal anesthesia complication characterized by pain in the buttocks, legs and the back).

# Skeletal Muscle Relaxants

## ➢ History:-

- *During* the **16th century, European explorers** ***found*** the *Native American* in **Amazon Basin** of **South America** were ***using*** **Curare**, an **arrow poison** that ***produced*** **skeletal muscle paralysis**, to ***kill*** **animals**.

- ***This poison***, known today as **Curare**. Its active ingredient, **Tubocurarine**, (***neuromuscular blocker***).
- **Tubocurarine** ***block*** **nicotinic acetylcholine receptors**, at the ***neuromuscular junction***.
- ***By 1943***, **neuromuscular blockers** became ***used*** as **muscle relaxants** in the **anesthesia** and **surgery**.

## ➢ Overview:-

- **Muscle relaxants** are ***two major*** **groups**, **Neuromuscular Blockers** and **Spasmolytics**;
  - **Neuromuscular blockers (NMBs)** act by ***blocking*** **nicotinic acetylcholine receptors** at the ***neuromuscular junction*** and have **no CNS activity**, they are often ***used*** **during surgical procedures** and in **intensive care**.
  - **Spasmolytics**; are ***centrally acting*** **muscle relaxants**, are ***used*** to **relief spasms** (*musculoskeletal pain*) and **spasticity** (*neurological conditions*).

## ➢ Spasticity and Spasms:-

- **Muscle Spasticity**; **Muscle tone** ***caused by*** **brain** or **spinal problems**, ***such as*** **cerebral palsy** and **multiple sclerosis**.
  - ***Treated by***; **Antispastic drugs**, **Baclofen**, **Tizanidine** (*first line*) and **Dantrolene** and **Diazepam** (*second line*), **Botulinum toxin** (Botox®) have been shown to be ***effective***.
- **Muscle Spasms**; **Muscle tone** ***caused by*** **musculoskeletal conditions**, ***such as*** **back** and **neck pain** and **fibromyalgia**.
  - ***Treated by***; **Antispasmodic drugs** ***such as*** **Cyclobenzaprine** and **Orphenadrine**.

## ➢ Classifications:-

- **Centrally Acting** (**Spasmolytics**);
  - *Such as*; **Diazepam**, **Baclofen**, **Tizanidine** and **Cyclobenzaprine**.
- **Peripherally Acting** (**Neuromuscular Blockers**);
  - *Such as*; **Succinylcholine**, **Pancuronium**, **Rocuronium** and **Vecuronium**.
- **Direct Acting**;
  - **Dantrolene**.

## A) Centrally Acting Skeletal Muscle Relaxants

### Centrally Antispasticity Agents

### Diazepam (Valium®)

- **Diazepam** ***facilitate*** the **action** of **GABA** in the **CNS** (*both* **brain** and **spinal cord**).
- **Diazepam** has been ***effective*** for **short-term use**, **tolerance** and **addiction** ***can occur***.
- **Benzodiazepines** in ***general*** are **used** as **anxiolytics**, **sedatives**, **hypnotics**, **anticonvulsants**, and/or **skeletal muscle relaxants** (**spasmolytics**).
- ***Dose***; usual adult dose of **Diazepam** for **muscle spasms*** and **muscle spasticity*** (**antispasmodic** and **antispasticity agent**); 2-10 mg orally 3-4 times daily, OR 5-10 mg IV/IM initially.
- ***Other*** **benzodiazepines** *may* be **used** as **spasmolytics**, ***but*** **clinical experience** with them is ***limited***.

## Baclofen (Lioresal®)

- **Baclofen** [BAK-loe-fen] is a ***derivative*** of **GABA** (*chlorophenyl*-**GABA**) **antispasticity agent**, was ***designed*** to be an **orally active GABA-*potentiating agent*.**
- **Baclofen** is an ***agonist*** at **GABA$_B$ receptors**, ***hyperpolarization*** (↑ $K^+$) ⇨ ***presynaptic*** **↓ calcium influx** and ↓ ***release*** of **excitatory transmitters** in CNS (*both* **brain** and **spinal cord**) ⇨ **↓ muscle tone** *as well as* **pain** *associated with* **spasticity**.
- ***Pharmacokinetics***; It is ***rapidly*** and ***completely*** **absorbed** *after* **oral administration** and has a plasma **half-life** of **3-4 hours**. **Baclofen** ***intrathecally*** (**3rd line therapy** in **MS spasticity**) ***may*** be **used**. It is primarily ***excreted*** **unchanged renally** (**used *with caution*** in **impaired renal function**).
- ***Uses***; It is ***primarily*** **used** for the ***treatment*** of **muscle spasticity***, ***especially*** in instances of **spinal cord injury (SCI)**, **cerebral palsy** and **multiple sclerosis (MS)**.
- ***Dose***; 5 mg 3 times daily for 3 days ⇨ 10 mg 3 times daily for 3 days ⇨ 15 mg 3 times daily for 3 days ⇨ 20 mg 3 times daily for 3 days (Max, 80 mg daily).
- ***Side effects***; **confusion, headache, insomnia, nausea, constipation** & ***increase*** **urinary frequency**.
- ***Warning***; ***Abrupt*** **discontinuation** of **Baclofen** can be ***associated with*** a **withdrawal syndrome**; **hallucinations** and **seizures**.

## Tizanidine (Sirdalud®)

- **Tizanidine** [tye-ZAN-i-deen] is a ***centrally acting*** **$\alpha_2$ adrenergic agonist** (as **Clonidine**), is an **antispasticity agent.**
- **Tizanidine** ***reduce*** **spasticity** at ***doses*** that *cause* ***fewer*** **cardiovascular effects** ***than*** **Clonidine.**
- ***Uses***; Like **Baclofen** it is ***primarily*** **used** for the ***treatment*** of **muscle spasticity*** (***some*** **physicians *used*** **Tizanidine** in **muscle spasms**).
- ***Dose***; ***Initial***; 2mg orally 3-4 times daily, ***maintenance***; 8mg orally 3-4 times daily, ***max.***; 36mg/day.
- ***Side effects***; **hypotension**, **sedation** and **dry mouth** (*dose-related*).
- ***Warning***; **Hepatotoxicity** (*monitor liver function tests*) and **abrupt discontinuation** can be associated with **rebound hypertension.**
- ***Drug interactions***; **CYP1A2 inhibitors,** *such as* **Ciprofloxacin** and **Fluvoxamine.**

## Centrally Antispasmodic Agents

## Orphenadrine (Norflex®)

- **Orphenadrine** [ore-FEN-uh-dreen] is an ***anticholinergic drug*** *closely related to* **Diphenhydramine**
- **Orphenadrine** is the ***first*** **agent** used in the ***treatment*** of **Parkinson's disease** in **1940s**.
- ***Mechanism of action***; The ***exact mechanism*** remains **unknown**, but may due to ***anticholinergic activity*** in **brain stem** (**analgesic *properties***).
- ***Metabolism***; by **CYP450**.
- ***Uses***; as an ***adjunct*** to **rest**, **physical therapy** and ***other*** **measures** for the ***relief*** **muscle spasms*** *associated with* ***acute painful*** **musculoskeletal conditions**.
- **Orphenadrine** also ***combine*** with analgesics; **NSAIDs** (**Aspirin** + **Caffeine**; Norgesic Forte®) or with **Paracetamol** (Norgesic®).
- ***Common Side effects***; **Confusion**, **constipation**, and **urinary retention** (*Anticholinergic effects*).

## Cyclobenzaprine (Flexeril®) (Multi-Relax®)

- **Cyclobenzaprine** [sye-kloe-BEN-za-preen] is ***structurally related*** to **tricyclic antidepressants**.
- ***Mechanism of action***; **Cyclobenzaprine** as a **muscle relaxant** is ***not fully understood***, but it is thought to act as **5-HT$_2$ receptor *antagonist*.** **Cyclobenzaprine** *exhibits* **anticholinergic activity.**
- ***Metabolism***; primarily by **CYP3A4** and **CYP1A2**.
- ***Uses***; It is ***approved*** for **muscle spasms*** *associated with* ***acute*** **musculoskeletal conditions**, It is often used ***off-label*** for **fibromyalgia**.
- ***Dose***; ***Initial***; 5 mg orally 3 times a day (***max.***; 10 mg orally 3 times a day).
- ***Side effects***; **Drowsiness**, **dry mouth** (*Anticholinergic effects*), **fatigue** and **headache**.
- ***Precautions***; ***Use in*** the **elderly** and **patients** *with* **hepatic dysfunction**.
- ***Drug interactions***; **MAO inhibitors** (or *within* **14 days** *after discontinuation*).
- ***Risk***; **serotonin syndrome**.

## Carisoprodol (Soma®) (Myorelax®)

- **Carisoprodol** [kar-eye-soe-PROE-dole] is a ***carbamate derivative***.
- ***Mechanism of action***; the ***exact mechanism*** remains **unknown**, but it may ***associated with*** causing **CNS depression** *resulting in* **sedation** and ***alteration*** in **pain perception**.
- ***Uses***; **Muscle spasms*** *associated with* ***acute painful*** **musculoskeletal conditions**.
- ***Metabolism***; Extensively metabolized by **CYP2C19**, one of its metabolites, **Meprobamate**, is an ***anxiolytic agent*** (**Meprobamate** is a drug of **abuse** and **dependence**)
- ***Effects***; **analgesia, anxiolytic, muscle relaxation, sedation** and **somnolence**.
- ***Dose***; 250-350 mg orally 3 times a daily.
- ***Side effects***; **Drowsiness** and **dizziness** (*CNS depression*).
- ***Precautions***; ***Use*** **patients** *with* **renal** or **hepatic dysfunction**.
- ***Warning***; **Abuse, dependence** and **withdrawal**.

## Methocarbamol (Robaxin®)

- **Methocarbamol** [meth-oh-KAR-ba-mal] is a ***carbamate derivative*** of **Guaifenesin** (*expectorant*).
- ***Mechanism of action***; Like **Carisoprodol**, remains **unknown**, but may be ***due*** to ***general*** **CNS depression**.
- ***Uses***; as an ***adjunct*** to **rest, physical therapy** and ***other*** **measures** for the ***relief*** **muscle spasms*** *associated with* ***acute painful*** **musculoskeletal conditions, and** ***control*** of **neuromuscular manifestations** of **tetanus**.
- **Methocarbamol** also ***combine*** with analgesics; **NSAIDs** (**Ibuprofen**; Ibuflex®, **Diclofenac Potassium**; Dimra®) or with **Paracetamol** (Methorelax®).
- ***Metabolism***; by **dealkylation** and **hydroxylation** and **conjugation** (*unlike* **Carisoprodol**, **Methocarbamol metabolites** ***not*** has **greatly abuse potential**).
- ***Formulations***; **oral** and **parenteral**.
- ***Dose***; ***Initial***; 1500 mg orally 4 times daily for the first 2 to 3 days, ***followed by*** 750 mg orally 4 times daily.
- ***Side effects***; **lightheadedness, dizziness** and **drowsiness**.
- ***N.B.***; **black, brown** or **green urine** are ***possible***.

## Metaxalone (Skelaxin®)

- **Metaxalone** [me-TAX-a-lone] is a ***muscle relaxant*** agent.
- ***Mechanism of action***; **unknown**, but may be ***due*** to ***general*** **CNS depression**.
- ***Uses***; as an ***adjunct***, for the ***relief*** **muscle spasms*** *associated with* ***acute painful*** **musculoskeletal conditions**.
- ***Metabolism***; by **CYP450**.
- ***Dose***; 800 mg 3-4 times daily.
- ***Side effects***; **Drowsiness, dizziness, nausea** and **vomiting**.
- ***Contraindications***; ***severe*** **hepatic** and **renal dysfunction**.

## Chlorzoxazone (Parafon®) (Myofen®)

- **Chlorzoxazone** [klor-ZOX-a-zone] is a ***muscle relaxant*** **agent**.
- ***Mechanism of action***; ***Not fully understood***, but it ***works*** **primarily** in **spinal cord** and **subcortical areas** of the brain ⇨ ***inhibits*** **multi-synaptic reflex arcs** involved in ***producing*** and ***maintaining*** **skeletal muscle spasm**.
- ***Uses***; **symptomatic** ***treatment*** of **muscle spasms*** and **pain** *associated with* ***acute painful*** **musculoskeletal conditions**.
- **Chlorzoxazone** is ***available*** in a ***combination*** with **analgesics** to ***relief*** **pain** *associated with* **muscle spasms**; **NSAIDs** (**Ibuprofen**; Myofen®) or with **Paracetamol** (Parafon® - Myolgin®).
- ***Dose***; 250-750 mg orally 3 to 4 times daily.
- ***Side effects***; **Dizziness, lightheadedness, malaise, nausea** and **vomiting**.
- ***Warning***; **Serious** (or **fatal**) **hepatocellular toxicity**, ***especially*** if used with **Paracetamol**.

# B) Peripherally Acting Skeletal Muscle Relaxants

## Neuromuscular Blockers (NMBs)

- These drugs **block cholinergic transmission** between ***motor nerve endings*** and the ***nicotinic receptors on the skeletal muscle.***
- NMBs are clinically useful **during surgery** to provide ***complete muscle relaxation.***
- NMBs *pharmacology are full discussed in Autonomic chapter.*

## Botulinum Toxin (BTX)

### *Clostridium botulinum* toxin type A (Botox®)

- **Botulinum toxin** is a ***neurotoxic*** **protein** *produced by* the **bacterium *Clostridium botulinum.***
- **Botulinum toxin** is the ***most powerful*** **neurotoxin** *known to date* (Only one single molecule of it is needed to stop one neuron working. *In fact*, 1 gram of botulinum toxin would be enough to kill 14,000 people (if ingested), 1.25 million people if inhaled, or a staggering 8.3 million people if injected).
- ***Clostridium botulinum*** is an **anaerobic, Gram positive, spore-*forming* rod.**
- **Botulinum toxin** acts by ***blocking*** **nerve function** by ***inhibition*** **Acetylcholine** ***release*** from the **presynaptic neuromuscular junctions**. This causes **skeletal muscle *paralysis*** and **respiratory failure** by paralysing the muscles of the chest.
- There are **2 commercial types** of **BTX**; **Botulinum toxin type A** and **Botulinum toxin type B.**
- ***Most common applications*** (***Uses***) or **Botulinum toxin type A** (Botox®);
  - **Cosmetics**; ***Prevent*** **development** of **wrinkles** by paralyzing facial muscles.
  - **Medical uses**; **Muscle spasticity***, **dystonia**, **overactive bladder**, **chronic migraine**, **axillary hyperhidrosis**, **blepharospasm**, **strabismus**, and **anal fissure.**
- **Botulinum toxin type B** (Myobloc®); used in **cervical dystonia.**
- **Heptavalent Botulism AntiToxin** (**HBAT**); was approved in 2010 as **botulism anti-toxin** that effectively neutralizes all 7 known botulinum nerve toxin serotypes (types A, B, C, D, E, F and G).

# C) Direct Acting Skeletal Muscle Relaxants

### Dantrolene (Dantrium®) (DantRelax®)

- **Dantrolene** [DAN-troe-leen] is a ***hydantoin derivative*** related to **Phenytoin** that has a ***unique peripheral mechanism*** of ***spasmolytic activity.***
- ***Mechanism of action***; **Dantrolene** is the ***only*** (***unique***) **drug** available that ***inhibits*** $Ca^{2+}$ ions ***release*** from **sarcoplasmic reticulum.**
- ***Uses***; - ***Treatment*** of **chronic muscle spasticity*** of upper **neuronal disorders,** including spinal cord injury, multiple sclerosis, and cerebral palsy.
    - ***Dose***; 25 mg orally once daily for 7 days, then 25 mg three times a day for 7 days, then 50 mg three times a day for 7 days, then 100 mg three times a day.
  - **Malignant hyperthermia**;
    - ***Dose***; **IV**; bolus 2.5 mg/kg, then 1 mg/kg IV every 4-6hr OR 0.25 mg/kg/hr IV infusion.
- ***Most common side effects***; drowsiness, dizziness, fatigue and diarrhea.
- ***Black box warning***; ***potential for*** **hepatotoxicity.**

➢ **Clinical Recommendations:-**

- There is ***no*** **clear evidence** that ***one*** **skeletal muscle relaxant** is ***superior*** to ***another*** for **musculoskeletal spasms.**
- **Skeletal muscle relaxants** are ***not considered*** **first-line therapy** for **musculoskeletal conditions.** The American Pain Society and the American College of Physicians *recommend* using **Paracetamol** and **NSAIDs** as ***first-line agents*** for ***acute*** **low back pain.**
- **Antispasmodic agents *should be* used *short-term*** (**two weeks**) for **acute low back pain.**
- ***Choice*** of **skeletal muscle relaxant** *should be* ***based on*** **individual drug characteristics** and **patient situation.**

# CNS Stimulants

- **Overview:-**
  - **CNS Stimulants**; are a **groups** of **drugs** that *alters* **activity** *within* the CNS.
  - *Classifications*;
    - *According to, Effects*;

A) **Psychomotor Stimulants**;

- These are **psychoactive drugs** that induce ***temporary* improvements** in *either* **mental** or **physical functions** or **both**, such as Caffeine and Nicotine.

B) **Psychotomimetic Drugs** (**Hallucinogens**);

- These drugs produce **hallucinations** by altering the perception of the surrounding environment, such as Lysergic Acid Diethylamide (LSD).

C) **Convulsants** & **Respiratory Stimulants**;

- These drugs have ***no clinical*** **application** and are often ***used*** in **poisons**, in **intensive care** and for **research**, such as Picrotoxin and Strychnine.

- *According to, Site of Actions*;

A) **Cerebral Stimulants**; e.g. **Methylxanthines** (Caffeine and Theophylline)
B) **Medullary** (or **Brain Stem**) **Stimulants**; **Analeptics** e.g. Picrotoxin.
C) **Spinal Cord Stimulants**; e.g. Strychnine.

## A) Psychomotor Stimulants

### 1) Methylxanthines

| Caffeine | Theophylline | Theobromine |
|---|---|---|

- Caffeine [kaf-EEN], Theophylline [thee-OFF-i-lin] and Theobromine [thee-oh-BROE-meen], are **methylxanthines** (*methylated* xanthines) ***natural* plant alkaloids origin** (**Tea, coffee** and **cocoa**).
- Caffeine is the ***most widely consumed* stimulant** in the **world**, is *found in* ***highest* concentration** in **coffee**, but it is also present in **tea, cola drinks, energy drinks, chocolate** and **cocoa**.
- Theophylline is *found in* **tea** and Theobromine is *found in* ***Theobroma cacao***.

**Mechanism OF Action**

- **Methylxanthines** have ***several* mechanisms**, the ***main* mechanisms** are;
  - * ***Inhibits* phosphodiesterase enzyme** ⇨ ***increase* cyclic adenosine monophosphate** (**cAMP**);
    - *In* **smooth muscle** ⇨ ↓ **contraction** (bronchodilatation).
    - *In* **cardiac muscle** ⇨ ↑ **contraction** (↑ **heart rate**).
  - * ***Block* adenosine receptors**;
    - *In* **heart** ⇨ ↑ **heart rate**.
    - *In* **brain** ⇨ **Stimulant effect**.

**Pharmaco Kinetics**

- ***Absorption***; ***Well absorbed*** **orally**.
- ***Distribution***; ***Throughout*** the **body** (brain, placenta and mother's milk).
- ***Metabolism***; ***Primary*** by the **CYP1A2**.
- ***Elimination***; **Urinary excretion**.

**Pharmacological Action**

- **100-200 mg** of Caffeine (1-2 cups [1= 237mL] of coffee);
  - ↓ Fatigue.
  - ↑ Mental alertness (*cerebral cortex stimulation*).
- **1.5 g** of Caffeine (12-15 cups of coffee);
  - ***Produces*** **anxiety** and **tremors**.
- **2-5 g** of Caffeine; **spinal cord *stimulation***.
- **Tolerance** can ***rapidly*** **develop** and **withdrawal symptoms** are **fatigue** and **sedation**.

# 3) Varenicline

## **Varenicline** (Chantix®) (Champix®)

- Chantix® in the USA and Champix® in Canada Europe and other countries.
- **Varenicline** [var-EN-ih-kleen] is an **oral drug** ***used*** ***to*** **quit smoking *(treat nicotine addiction)*.** ***Act as*** a **partial agonist** in the **nicotinic receptors** (especially CNS).

**Dose**

- Days 1 to 3 ⇨ 0.5 mg orally once a day.
- Days 4 to 7 ⇨ 0.5 mg orally twice a day.
- Days 8 to end of treatment ⇨ 1 mg orally twice a day.

☞ Patients should be treated with **Varenicline** for 12 weeks.

- ***Most common adverse effects*** ☞ **Nausea, vomiting, headache, constipation, sleep disturbance** and **unusual dreams**. **Varenicline** are **category C *in pregnancy***.
- In 2007, the FDA received post-marketing reports of thoughts of suicide in people using **Varenicline**.
- In 2009, the FDA requires **Varenicline** to carry a **black box *warning*** that the drug should be stopped if suicidal behaviour are developed.

# 4) Cocaine

## Cocaine

- **Cocaine** [koe-KANE] is a ***strong*** **CNS stimulant *derived from*** the **coca plant.**
- **Cocaine** is a ***widely available*** **illegal drug** and ***highly*** **addictive drug**.
- ***Topical*** **Cocaine** can be ***used as*** **local anesthetic.**

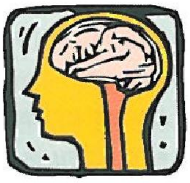
**Mechanism OF Action**

- It ***inhibits*** **reuptake** of **Serotonin, Norepinephrine** and **Dopamine** (***Serotonin Norepinephrine Dopamine Reuptake Inhibitor***; ***SNDRI***).
- It also ***blocks*** **sodium channels** (***local anesthetic***).

**Pharmaco Kinetics**

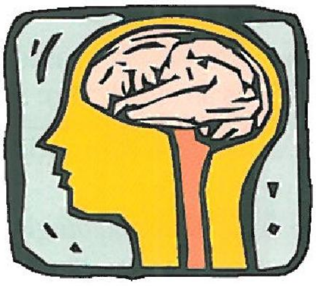
- ***Routes of illicit administration***; **smoking, snorting** and **IV**.
- ***Absorption***; ***Highly*** **lipid soluble** (**oral** and **GI mucosa, lungs**, and **skin**).
- ***Distribution***; ***Throughout the body*** (brain, placenta and mother's milk).
- ***Metabolism***; By **hydrolysis** to a ***variety*** of **compounds**.
- ***Elimination***; **Urinary *excretion***.

**Pharmacological Action**



- ***Feeling*** of **well-being** and **euphoria**.
- ***Increase*** **attention sexual excitement**, ***promotes*** **talkativeness**, ***enhance*** **mental alertness** and **learning**.
- At ***higher*** **doses** or **chronic use; euphoria** may be ***replaced with*** **restlessness, sleeplessness**, ***loss*** of **libido, nervousness, hallucinations** and **delusion.**

- ***Increase*** **heart rate** and **blood pressure.**
- ***Increase*** **body temperature.**
- ***Dilated*** **pupils** (**mydriasis**) & ***increase*** **light sensitivity.**



- **Cocaine** ***overdose***;
  - **Agitation**, ***enhance*** **reflexes** and **headache.**
  - **Tachycardia** and ***irregular*** **respiration**
  - ***Rise*** in **body temperature, nausea** and **vomiting.**
  - **Hallucinations, convulsions, delirium** and **seizures.**
  - **Stroke** or **cerebral hemorrhage.**
  - **Heart failure** and ***death*** from **respiratory failure.**
- **Cocaine** is a ***powerfully*** **addictive drug** of **abuse** and ***withdrawal symptoms*** are ***rapidly*** **developed *after*** **discontinuation.**

# 5) Amphetamines

## Amphetamine (Adderall®)

- **Amphetamine** [am-FET-a-meen] is a ***potent CNS stimulant.***
- **Amphetamine** is ***medically used*** in the ***treatment*** of **attention deficit hyperactivity disorder (ADHD), narcolepsy** and **obesity**.
- **Amphetamine** is also ***abused*** as a **performance** and **cognitive enhancer** and ***recreationally*** as an **aphrodisiac** and **euphoriant**.
- **Amphetamines *may cause*, dependence** and **tolerance**.

**Mechanism OF Action**

- **Amphetamine** and ***amphetamine-like*** **drugs** are ***sympathomimetic*** **amines** with **CNS stimulant *activity*.**
- **Amphetamine** act in **CNS** and **peripheral nervous system** as ***indirect increase*** **release** and ***decrease*** **reuptake** of **monoamines** (**Serotonin**, **Norepinephrine** and **Dopamine**).

**Pharmaco Kinetics**

- ***Routes of illicit administration***; **smoking** and **IV**.
- ***Absorption***; ***Completely*** **absorbed** *from* **GIT**.
- ***Distribution***; ***Throughout the body*** (brain, placenta and mother's milk).
- ***Metabolism***; By the **liver**.
- ***Elimination***; **Urinary *excretion*.**

**Pharmacological Action**

- ***Feeling*** of ***wakefulness*** and ***euphoria.***
- ***Increase alertness*** and ***decrease fatigue.***
- ***Slight analgesic effect.***
- ***Anorexigenic effect*** (*loss of appetite*).

- ***Increase*** **heart rate** and **blood pressure.**
- **Urinary *retention*.**
- **Nausea, vomiting** and **diarrhea** or **constipation.**

**Side Effects**

- ***Cardiovascular side effects***; **Tachycardia** and ***increase*** **blood pressure.**
- ***CNS side effects***; **Insomnia, anxiety, hallucination** and **tremor.**
- ***Other side effects***; **Weight loss, bladder pain** (*painful urination*), **headache, nausea, vomiting, abdominal cramps** and **diarrhea** or **constipation.**

## Amphetamine Derivatives

### Dextroamphetamine (Dexedrine®) | Lisdexamfetamine (Vyvanse®)

- **Dextroamphetamine** [DEX-troe-am-FET-a-meen] is the ***more active*** (*dextrorotatory*) **enantiomer** of the **Amphetamine. Lisdexamfetamine** [lis-dex-am-FET-a-meen] is a **prodrug** that is ***converted to*** the **Dextroamphetamine.**

### Methamphetamine (Desoxyn®)

- **Methamphetamine** [meth-am-FETa-meen], *known as* "**speed**".
- It is like **Amphetamine** *but*; ***much*** **stronger**, ***act*** **quicker** and ***more*** **addicting.**

### Methylphenidate (Ritalin®)

- **Methylphenidate** [meth-ill-FEN-ih-date] ***like*** **Amphetamine** with ***less*** **side effects.**
- **Addiction** and **psychological dependence** are ***rare.***

### Modafinil (Provigil®)

- **Modafinil** [moe-DAF-i-nil] is a ***wakefulness-promoting agent***, ***used*** in **sleep disorders.**

### Fenethylline (Captagon®)

- **Fenethylline** is a ***prodrug***, it is ***metabolized to***; **amphetamine** and **theophylline.**
- ***Most*** of the ***amphetamines*** **abused** in **Saudi Arabia** and other **Arab countries.**

# Drugs of Abuse

- A **boy** *sniffing* **glue** to *escape from* his **poverty**.
- A *new* **gang** *member* **smokes** *with his friends* to *feel like* he **belongs**.
- A *curious* **girl** *swallows* a **Molly** (*pure powder of* **MDMA**) to *see* **what it is like**.
- A *lonely* **widower** *drinks* to *help* *remember* the **past** and *forget* the **present**.
- *In each of these* **cases**, **chemicals** are being **used** for *non*-**therapeutic effects** on the **mind** or **body**.

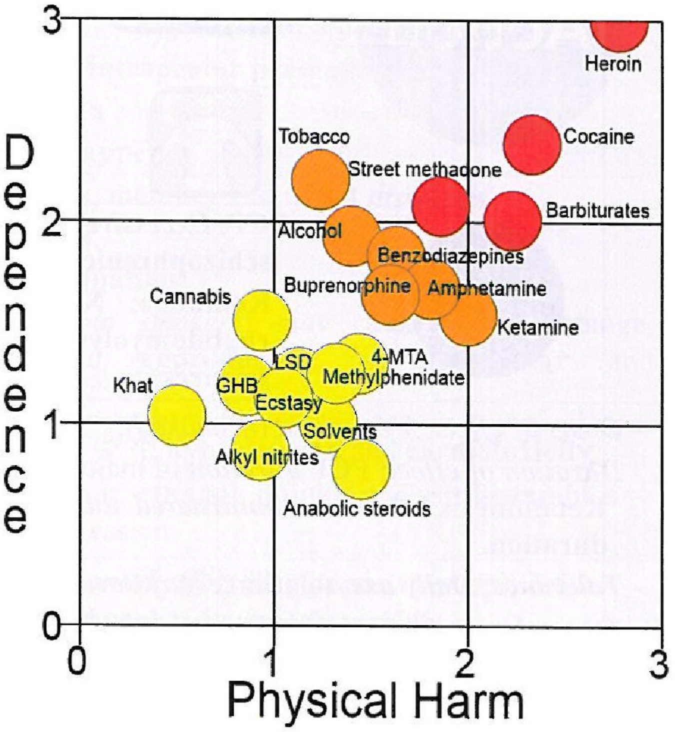
Boys are Sniffing Glue

- *Excessive* **misuse** of **drugs** is *considered* **substance abuse**.
- **In 2012**, about **24 million** *persons* in the **United States**, *aged* **12 years** and **older**, were *current* **users** of *some form* of **illicit substance**.

➢ **Common Abused Drugs:-**

- **Alcohol**
- **Alkyl nitrites** (**Poppers**)
- **Amphetamine** (1)
- **Anabolic Steroids**
- **Ayahuasca** (**DMT** *containing plants*)
- **Barbiturates** (2)
- **Benzodiazepines** (3)
- **Cannabis/Marijuana/Hashish** (4)
- **Cocaine** (5)
- **Dextromethorphan**
- **Dimethyltryptamine** (**DMT**)
- **Gamma-hydroxybutyric acid** (**GHB**)
- **Heroin** (6)
- **Ketamine** (7)
- **Khat** (*Catha edulis*)
- **Kratom** (*Mitragyna speciosa*)
- **Lysergic Acid Diethylamide** (**LSD**) (8)
- **MDMA** (*Ecstasy/Molly*)
- **Mescaline** (9)
- **Methamphetamine** (10)
- **Phencyclidine** (**PCP**) (11)
- **Psilocybin** (12)
- **Rohypnol**® (**Flunitrazepam**)
- **Salvia** (*Salvia divinorum*)
- **Scorpions** and **Lizards**
- **Synthetic Cannabinoids** (13)
- **Synthetic Cathinones**
- **Tobacco** (14)
- **Voodoo**

🟩 *Plant origin*
🟥 *Drug class*
🟦 *Generic drug name*
⬛ *Others*



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(13); *See page no. 416.*
(14); *See page no. 411.*

➢ **Common Club** (or **Rave**) **Drugs:-**

- **MDMA** (*Ecstasy/Molly*)
- **Ketamine** (7)
- **Lysergic Acid Diethylamide** (**LSD**) (8)
- **Methamphetamine** (10)
- **Gamma-hydroxybutyric acid** (**GHB**)
- **Rohypnol**® (**Flunitrazepam**)

## Methylene-dioxy-methamphetamine (MDMA) (Ecstasy) (Molly)

Ecstasy Tablets

- **Methylenedioxymethamphetamine (MDMA)**, ***commonly known as*** "**Ecstasy**", is a ***psychoactive drug*** **used *primarily*** as a **recreational drug**.
- **MDMA** is the **methylene-dioxy *derivative*** of **Methamphetamine** (*Amphetamines*).
- **MDMA** was ***first made*** in **1912**. It was ***used*** to ***improve*** **psychotherapy** in the **1970s** and become popular as a ***street drug*** in the **1980s**.
- **MDMA** is **commonly *associated with*** **dance parties** and **dance music** "**club drugs**".
- *In 2013*, ***between* 9** and **28 million people *between*** the **ages** of **15** and **65 used ecstasy** (0.2% to 0.6% of the world population).
- ***Street names***; **Ecstasy**, **E**, **X**, **XTC**, **Adam**, **Clarity**, **Lover's Speed** and **disco biscuit**.
- **Molly** is a ***pure powder*** of **MDMA** (**Ecstasy** ***usually refers*** to a **MDMA** ***pill form***).
- ***Mechanism of Action***; ***Similar*** to the **Amphetamines**, **MDMA** causes ***release*** of **monoamines** (**Serotonin**, **Norepinephrine** and **Dopamine**), **MDMA** also has ***weak*** **agonist activity** at **postsynaptic serotonin 5-HT$_2$ receptors**.
- ***Routes of Administration***; *Primarily* by **oral administration**, **MDMA** may be ***dissolved*** and **injected**, or ***crushed*** and **snorted**.

**Pharmacological Action**

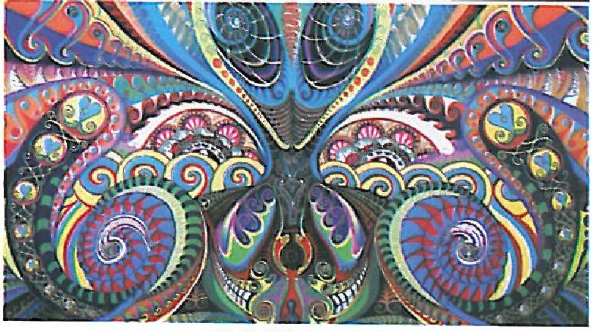
- ***Low*** to ***moderate*** **doses** (50-200 mg); ***Feelings*** of **well-being** and **euphoria**, ***increase*** **physical** and **emotional energy**, ***increase*** **sociability** and ***increase*** **responsiveness** to **touch**.
- ***At higher*** **doses**; **agitation**, **panic attacks**, and **hallucination**.
- ***Mild*** **visual disturbances**, **mydriasis**, **dry mouth**, **sweating**, **ataxia** and **muscle tension**.

**Side Effects**

- ***Impairment*** of **cognitive**, **perception** and **mental associations**.
- **Flashbacks**, **panic attacks** and **psychosis**.
- **Confusion**, **depression**, ***severe*** **anxiety** and **paranoia**.
- **Hyperthermia** and **tachycardia**.

- ***Onset of effect***; **20-30 minutes**. ***Duration of effect***; ***General*** **effects** last for *approximately* **2-3 hours**. **MDMA** is *sometimes* used in **combination** with **LSD** to ***increase*** its **duration** of **effects**, ***unwanted effects*** are *generally* **lasts** for **24 hours**.
- ***Dependence***; **Ecstasy** is ***not*** **physically addictive** *in the way that drugs like* **Cocaine**, **Nicotine** and **Heroin**. ***Many users***, ***addicted to*** the **emotional state** they ***reach on*** the **drug**.

## Dimethyltryptamine (DMT)



DMT Vision Art

- **Dimethyltryptamine (DMT)** is a ***powerful psychedelic drug*** of **tryptamine family** & **serotonergic hallucinogen**.
- It is a **structural *analog*** of **Serotonin** & **Melatonin**.
- It also ***found*** in **several plant** (*See Ayahuasca*).
- It also ***occurs*** in ***trace*** **amounts** in ***mammalian*** **brain**, **blood** and **urine**.
- It is known to ***act as*** an **agonist** or **antagonist** of certain **serotonin receptors**.
- **DMT** was ***first*** **synthesized** in **1931**, **DMT** *produce* ***powerful*** **psychedelic experiences** including ***intense*** **visuals**, **euphoria** and **hallucinations**.

- *Street names*; **Dimitri, fantasia, businessman's special** and **blue elephant** (The blue elephant [novel/film]; is a Arabic novel written by the famous Egyptian writer Ahmed Mourad, describe DMT as a blue elephant shaped tablet used as a hallucinogen agent).

**Pharmaco Kinetics**

- **DMT** ***alone*** is ***not active*** **orally**, *because* it is ***rapidly*** **metabolized** by **monoamine oxidase (MAO) enzyme**, if **ingested** ***alone*** it has ***no*** **hallucinogenic effect** in ***normal doses*** (*dose not exceeds MAO metabolic capacity*).
- *So*, **DMT** is ***combined*** with a **monoamine oxidase** ***inhibitor*** **(MAOI)** such as a ***reversible inhibitor*** of **monoamine oxidase A**, such as **Harmaline**.
- *Routes of Administration*; *Primarily* by **oral administration**, **DMT** may be ***dissolved*** and **injected**, or ***crushed*** and **snorted**.

**Pharmacological Action**

- *Intense* **visual** and **auditory hallucinations** (fantasy or dream such as talking to supernatural beings, alien life-forms, traveling to different dimensions or otherwise intense and engaging hallucinations).
- ***Changes*** in **perception** *about* **body, surroundings**, & **time**.

- *Increase* **heart rate** and **blood pressure**.
- **Agitation** and **seizures**.
- **Mydriasis** and ***involuntary*** *rapid* **eye movements**.
- **Dizziness** and **incoordination**.

- **DMT** is also ***combined*** with **MAOI**; ***risk*** of **hypertensive crisis**, from eating **tyramine-*rich* foods**.
- *Onset of effect*; *Very rapid* **10-60 seconds** (*if smoked*). *Duration of effect*; **effects** *usually* **resolving** in **30-45 minutes** or *less*.
- *Dependence*; **DMT** is ***not*** **addictive**, ***but*** **many users**, ***addicted to*** the **fantasy state** of the drug.

## Ayahuasca

- **Ayahuasca**; is a ***hallucinogenic tea made in*** the **Amazon** from a **DMT-containing plant** (*Psychotria viridis* or *Diplopterys cabrerana* or other) with another plants containing MAO inhibitor (*Banisteriopsis caapi*) to ***preventing*** the **breakdown** of **DMT** in the *digestive system*.

Ayahuasca Preparing

Ayahuasca Cooking

Ayahuasca

## Gamma-Hydroxy Butyric (GHB) Acid

- **Gamma-hydroxybutyric acid** (**GHB**) is a ***naturally*** (***endogenous***) **occurring** is ***during*** the **metabolism** of **GABA**.
- **GHB** was ***first*** synthesized in **1960** and *introduced as* a **general anesthetic**, The ***only*** **use** for **GHB** today are in the ***treatment*** of **narcolepsy** and more rarely **alcoholism**.
- **Gamma-butyrolactone** (**GBL**) and **1,4 butanediol** (**1,4-BD**) are **GHB** ***prodrug***.
- *CNS effects* (*at low doses*); **effects** are ***similar to*** those seen with **Alcohol**. **Relaxation, euphoria, confusion, dizziness, drowsiness, sedation** and **hallucinations**.
- *Severe* **addiction** occurs with **chronic abuse**.

## Rohypnol® (Flunitrazepam)

- **Rohypnol®** is the **brand name** for a drug *called* **Flunitrazepam**; is an ***intermediate-acting*** **benzodiazepine**, which is a ***powerful*** **sedative**.
- **Rohypnol®** is also called "***Date rape drug***", i.e. *Drug Facilitated Sexual Assault* (*DFSA*) and "**Quaalude of the '90s**"
- **Quaalude®** is a **brand name** for **Methaqualone**, which was ***first synthesized*** in **1951**, with ***mechanism of action*** *similar* to **benzodiazepine.**
- **Quaalude®** were ***widely popular*** in the 1970s and 1980s as a ***party drug*** in **nightclubs**, and ***used as*** a **date rape drug**.
- *In* **1990s**; **Quaaludes®** is ***largely replaced by*** **Rohypnol®** "**Quaalude of the '90s**".
- **Rohypnol®** is a **drug of abuse** at **bars, nightclubs** and **parties** to **commit sexual assaults** by ***adding it*** to **Alcohol** or **juice**.
- ***Other*** **date rape drugs** *include*; **Ketamine** and **Gamma-hydroxy Butyrate** (**GHB**).

## Dextromethorphan

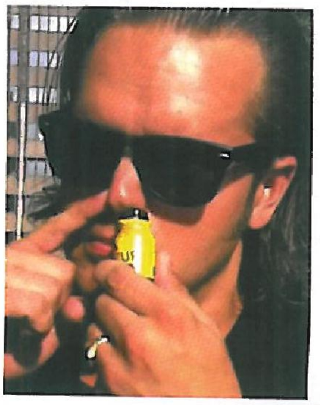
- **Dextromethorphan** (**DXM** or **DM**) is the ***dextrorotatory*** enantiomer of **Levomethorphan**, which is the ***methyl ether*** of **Levorphanol**, ***both*** **opioid analgesics**.
- It is ***one*** of the **active ingredients** in ***many*** **over-the-counter** (OTC) **cold** and **cough medicines**.
- The ***primary use*** of **Dextromethorphan** is as a **cough suppressant** (***antitussive***).
- ***Usual antitussive dose*** is **15-30 mg 3** or **4 times** ***daily***.
- At ***high*** **doses Dextromethorphan** acts as an **NMDA receptor** ***antagonist***.
- ***Recreational Doses***;
    - **100-200 mg**; ***Mild*** **stimulant effect** and ***mild*** **elevated mood**.
    - **200-500 mg**; ***Mild*** **hallucination** and ***acute*** **euphoria**.
    - **500-1000 mg**; **Hallucination** and ***mild*** **dissociate effect** (*likened to* a low dose of **Ketamine**).
    - **> 1000 mg**; ***Full*** **dissociative effect** (*likened to* a high dose of **Ketamine**).
- ***Side Effects***; At ***acute*** **high doses (250-1500 mg)**; excitation, nausea, vomiting, drowsiness, blurred vision, rash, ataxia, sweating, hot/cold flashes, fever, hypertension, urinary retention, diarrhea, psychosis, coma and increase heart rate, blood pressure and body temperature.
- ***Dependence***; At ***recommended*** **antitussive doses**, **addiction** does ***not occur***. ***Mild*** **psychological dependence** and **depression** *may* **occur** with ***regular*** **use** of ***increased*** **doses**.

## Alkyl Nitrites (Poppers) or Inhalant Abuse

- **Poppers** is a ***street name*** **given to** the ***chemical class*** called **alkyl nitrites** that are ***inhaled*** for **recreational uses**.
- ***Most widely used*** are; **Amyl Nitrite**, **Cyclohexyl Nitrite**, **Isobutyl Nitrite** and **Isopropyl Nitrite**.
- They were part of ***club culture*** from **70s** to **80s**.

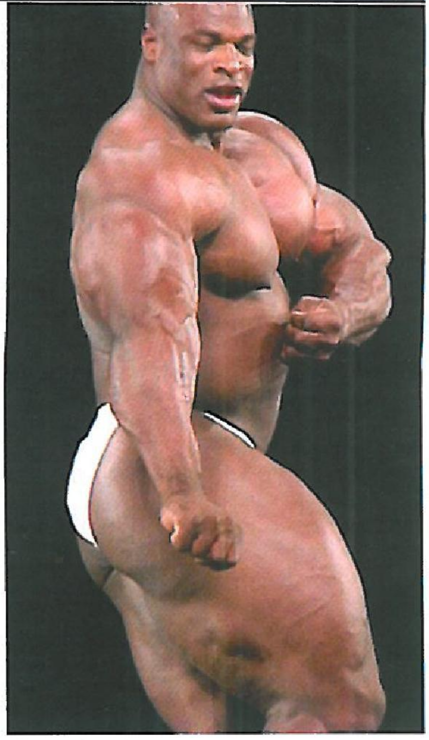
N
ROOM
ODORISER
RUSH
AROMA
Liquid Gold
PURPLE
HAZE
ROOM
ODORISER
Poppers

A selection of poppers



- ***In*** **1990s hallucination scene** ***made their*** **use** ***popular***.
- **Amyl nitrite** *was* **first** ***synthesized in*** **1844** and **used** to ***treat*** **angina pectoris**.
- ***Mechanism of action***; **Poppers** ***primarily*** produce **smooth muscle *relaxation*** and ***enhance*** **erection**, ***but*** are ***not*** **addictive**.
- **Poppers** are ***primarily*** **used** to ***enhance*** a **sexual activity**, and to ***facilitate*** **anal sex** in ***homosexual*** by **relaxing** the ***internal*** and ***external*** **anal sphincter muscles**.
- ***Overdose*** via **ingestion** (*rather than inhalation*) may result in **cyanosis**, **unconsciousness**, **coma** and ***even*** **death**.
- ***Side Effects***; **headache**.

## Anabolic Steroids


Ronnie Coleman (Gynecomastia)

- **Anabolic steroids** are *synthetic agents* of the **male sex hormone Testosterone**.
- **Anabolic steroids** are **used** *illegally* to *increase* **muscle mass**, *decrease* **fat** and *enhance* **athletic performance** and **body appearance**.
- The ***most* shocking consequences** of **steroid abuse**;

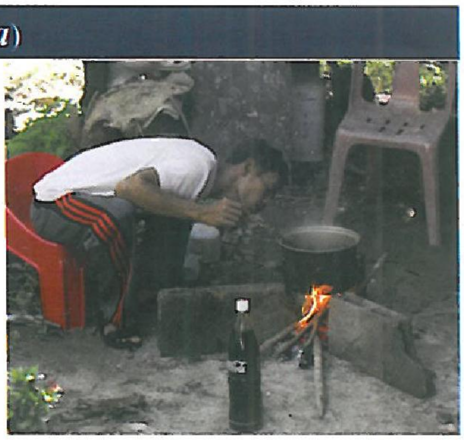
  1) **Turtle Belly** (*such as in* Markus Rühl).
  2) **Gynecomastia** (*such as in* Ronnie Coleman).
  3) **Hair loss and liver damage** (*such as in* Craig Davidson).
  4) **Heart/liver/kidney failure** (*such as in* Andreas Münzer).
  5) **Multiple organ failure** (*such as in* Matthew Dear).
  6) **Steroid withdrawal**; risk of suicide especially teenage.
  7) **Infections** (*such as in* Greg Valentino; infected bicep).
  8) **Sex change** (*such as in* Candice Armstrong).
  9) **Murder/Suicide** (*such as in* Chris Benoit).
- **Anabolic steroids** are ***usually*** **injected** ***into the*** **muscle**, ***but*** **some** ***are available*** in **tablet** or **cream** or **gel**.
- **Post Cycle Therapy** (**PCT**) is ***needed*** to ***re-regulate*** **normal hormone levels** in the **body**.

## Cathinones (Khat)

Yemeni man chewing khat

- **Cathinone** is a **monoamine alkaloid** found in *Catha edulis* (**khat**) in **East Africa** and the **Arabian Peninsula** (**Yemen, Ethiopia, Somalia** and ***other countries***).
- **Cathinone** has been found to **stimulate** ***release*** of **Dopamine** and ***inhibit*** **reuptake** of **Epinephrine**, **Norepinephrine** and **Serotonin** in a **manner** ***very similar*** to **Cocaine** and **Amphetamine**.
- **Synthetic Cathinones**, commonly known as "**bath salts**" are ***synthetic drugs*** **chemically** ***related to*** **Cathinone**.
- **Methcathinone**, **Butylone**, **Methylene dioxy-pyrovalerone**, and **Naphyrone** are just a few examples of synthetic **Cathinone**.
- **Synthetic Cathinones** are ***strong*** and ***more dangerous*** than **khat**.
- **Bath salts** are ***generally*** **snorted** or **ingested**, *but* they may also be **injected**.
- **General effects** are ***similar*** to **Amphetamine** and **Cocaine**.

## Kratom (*Mitragyna speciosa*)



- ***Mitragyna speciosa*** (**ketum** or **kratom**) is a **plant** ***found in*** **Southeast Asia** in the **Thailand**, **Indochina** and **Malaysia**.
- **Kratom** is ***not*** an **opiate itself**, but is thought to behave ***similar*** to an **μ-opioid receptor** ***agonist*** *like* **Morphine**.
- **Kratom** is used in the ***management*** of **chronic pain**.
- **Kratom** has been ***traditionally*** by **chewed** in ***raw leaf form*** or as **kratom tea** (**kratom leaves** are ***mixed with*** **cough syrup** and **Coca-Cola**).
- **Kratom** ***can be*** **addictive**.

## Voodoo

- **Voodoo** is a ***new*** **type** of **drug** that has ***recently*** **spread** in **Egypt** and ***other*** **countries**.
- **Voodoo** ***comes in*** **bags** ***containing*** a **mixture** of **herbs** of ***unknown sources***.
- It is *composed of* ***unknown*** **herbs** with a **smell** ***similar*** to **spices** and **incense**.
- These ***dried*** **herbs** are then ***sprayed with*** **synthetic cannabinoids** such as **JWH-018** (**analgesic cannabinoid**) and "**$\Delta^9$-Tetrahydrocannabinol**.
- The **Voodoo** drug ***affects*** the **brain** in the ***same way*** like **cannabis**.

Spice
DIAMOND

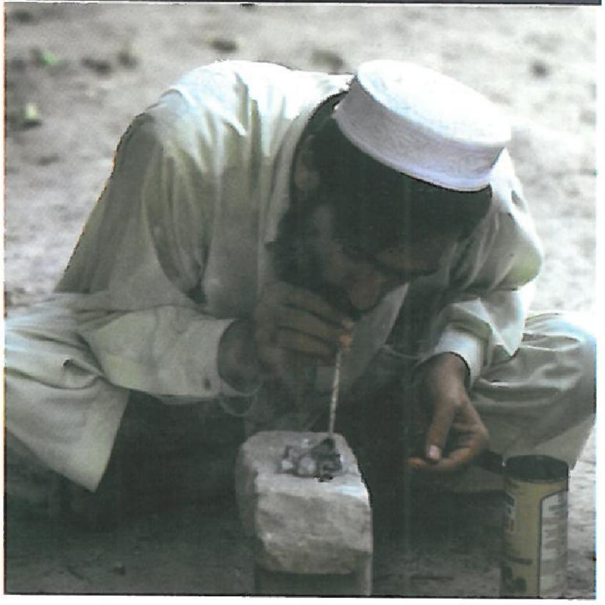
- The **Egyptian Ministry of Health** ***listed this*** **drug** in **schedule 1** and ***warned*** **traffickers** and **users** that they are now ***under*** **criminal penalties**.

## Salvia (*Salvia divinorum*)

- ***Salvia divinorum*** (**Salvia**) is a **plant** ***found in*** **Sierra Mazateca** of **Oaxaca, Mexico**.
- **Salvinorin A**, the ***main*** **active ingredient** in **salvia**, **Salvinorin A** is a ***potent*** and ***selective*** **kappa-opioid receptor** ***agonist***, However, it is a **$D_2$ receptor** ***partial agonist***.
- **Salvia** has been ***traditionally*** by **chewed** in ***raw leaf form***, **drink** ***leaves extract*** or **smoking**.
- ***Common CNS effects***; **Happiness, self-confidence, dissociation, visual effects, calmness** and **dizziness**.

## Scorpions and Lizards

- The **use** of ***various*** **insects** as **substances of abuse** has ***not*** **been reported** in ***detail*** in **medical**.
- The **Indian spiny tailed lizard** (*Uromastyx hardwickii*) found in **India** and **Pakistan**, is used as an **embrocation** and as a ***cure for*** **impotence**.
- A 25-year-old male prisoner, with a 15-year history of cannabis abuse, shifted his drug of abuse to lizards due to non-availability of cannabis in prison.
- ***Smoking*** **scorpions** has recently been gaining **popularity** in several parts of **Pakistan**.
- **People** who have ***tried smoking*** **dead scorpions** label it as the "**worst form of addiction**".
- ***Smoking dead scorpions*** causes ***short*** and ***long term*** **memory loss**, with ***high massive*** **hallucinations**.
- "**Scorpion Smoking**" *is the latest trend in the scary world of addiction*.



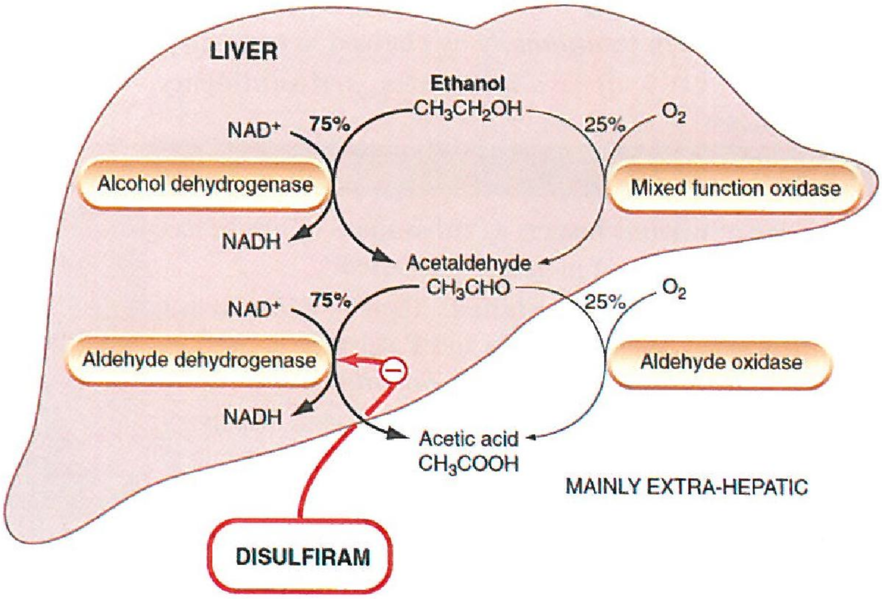
Pakistani man smoking scorpion

## Ethyl Alcohol (Ethanol)

- **Ethanol** is a *clear* colorless *hydroxylated* **hydrocarbon** that is the **product** of *fermentation* of **fruits, grains** or **vegetables**.
- **Alcohol** is the ***most commonly*** **abused substance** in **modern society**.
- In the **United States**, *approximately* **75%** of the **adult population** *drinks* **Alcohol** *regularly*.
- ***In 2013***, **139,000 deaths** ***globally*** were ***directly*** due to **alcohol abuse** and an additional **384,000** to **cirrhosis** from ***excess*** **alcohol consumption**.

**Pharmaco Kinetics**

- ***Absorption***; ***Rapidly*** from **GIT** (food in the **stomach** ***delays*** **absorption**).
- ***Distribution***; **Throughout the body** (brain, placenta and mother's milk).
- ***Metabolism***; ***Primary*** in the **liver**, and mainly by a pathway involving ***successive*** **oxidations**, ***first*** to **acetaldehyde** (**Alcohol dehydrogenase pathway**) and ***then*** to **acetic acid** (**Acetaldehyde dehydrogenase pathway**).


LIVER
Ethanol
$CH_3CH_2OH$
NAD+
75%
25%
$O_2$
Alcohol dehydrogenase
Mixed function oxidase
NADH
Acetaldehyde
$CH_3CHO$
NAD+
75%
25%
$O_2$
Aldehyde dehydrogenase
Aldehyde oxidase
NADH
Acetic acid
$CH_3COOH$
MAINLY EXTRA-HEPATIC
DISULFIRAM

- **Disulfiram** [dye-SUL-fi-ram] is a drug that ***blocks*** **oxidation** of **Acetaldehyde** to **Acetic acid** by ***inhibiting*** **aldehyde dehydrogenase**. It has been ***used to*** **deter drinking** by patients ***with*** **alcohol dependence**. **Ethanol** + **Disulfiram** ⇨ **Acetaldehyde** ***accumulates*** and **causes** an ***unpleasant*** **reaction** of **facial flushing, nausea, vomiting, dizziness** and **headache**. ***Several other drugs*** (e.g., **Metronidazole**, **Cefotetan** and **Trimethoprim**) ***inhibit*** **aldehyde dehydrogenase** and can cause a **Disulfiram *-like reaction*** if ***combined with*** **Ethanol**.
- ***In 50%*** of **Asian people**, an ***inactive*** **genetic variant** of one of the **aldehyde dehydrogenase** *isoforms* (ALDH-2) is expressed; ***these*** **individuals** *experience* a **Disulfiram *-like reaction*** after **Alcohol**, and the *incidence* of **alcoholism** in this group is *extremely* **low**.

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- **Ethanol** ***affects*** a **large number** of **membrane proteins** that ***participate in*** **signaling pathways**, *including* **neurotransmitter receptors**.
- ***Acute*** **Ethanol exposure** ***enhances*** the **action** of **GABA** at **GABA<sub>A</sub> receptors** and ***inhibition*** of **NMDA receptor** ***activation***.

## Pharmacological Action

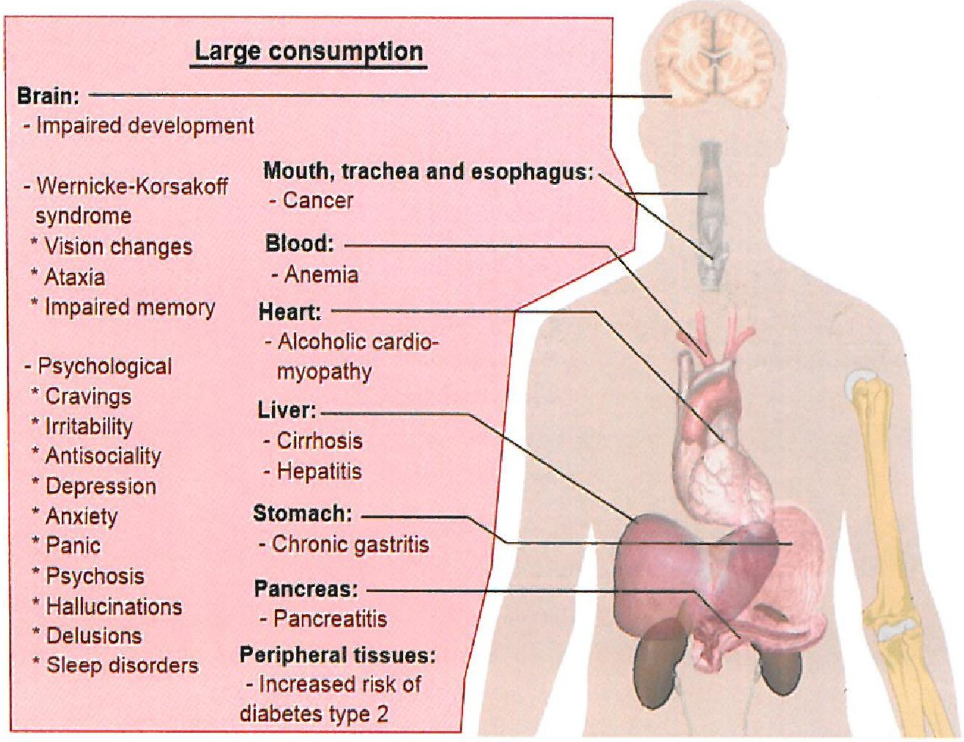
- Like *other* sedative-hypnotic drugs, **Alcohol** is a **CNS depressant**. At ***high*** **blood concentrations**, it ***induces*** **coma, respiratory depression**, and **death**.
- ***Blood alcohol concentration and clinical effects in nontolerant individuals***;
  - **50-100** mg/dL; **Sedation** and *relief* **anxiety**.
  - **100-200** mg/dL; ***Impaired*** **motor function, slurred speech** and **ataxia**.
  - **200-300** mg/dL; **Emesis** and **stupor**.
  - **300-400** mg/dL; **Coma**.
  - **> 400** mg/dL; **Respiratory depression, death**.

- ***Low*** to ***moderate*** **amounts** of **Alcohol** ***consumed*** (> 100 mg/dL); ***Significant*** **myocardial contractility** ***depression***.

## Toxicity

**A) Acute Alcohol Toxicity**;
- ***Severe*** **confusion** and **stupor**.
- **Vomiting**.
- **Seizures**.
- **Respiratory depression**.
- **Pale** and **clammy skin** (*insufficient oxygen*).

**B) Chronic Alcohol Toxicity**; ***Chronic*** **consumption** of ***large*** **amounts** of **Alcohol** is ***associated with*** an ***increased*** **risk of death** (**liver disease, cancer, accidents** and **suicide**).


Large consumption
Brain:
- Impaired development
- Wernicke-Korsakoff syndrome
* Vision changes
* Ataxia
* Impaired memory
- Psychological
* Cravings
* Irritability
* Antisociality
* Depression
* Anxiety
* Panic
* Psychosis
* Hallucinations
* Delusions
* Sleep disorders
Mouth, trachea and esophagus:
- Cancer
Blood:
- Anemia
Heart:
- Alcoholic cardio-myopathy
Liver:
- Cirrhosis
- Hepatitis
Stomach:
- Chronic gastritis
Pancreas:
- Pancreatitis
Peripheral tissues:
- Increased risk of diabetes type 2

CNS Revision

## Drug Interactions

- ***Acute consumption***; ***inhibit*** **metabolism** of **other drugs** (*decreased enzyme activity or decreased liver blood flow*), the ***most important drugs*** are; **Phenothiazines** (**Chlorpromazine**), **tricyclic antidepressants** (**Amitriptyline**), and **sedative-hypnotic drugs** (**Benzodiazepines**).
- ***Chronic consumption***; ***risk of*** **hepatotoxicity** *due to* ***toxic*** or *even* ***high*** **therapeutic levels** of **Paracetamol**.

- ***Treatment of alcohol dependence*** (*Medications*); **Disulfiram**, **Naltrexone** and **Acamprosate**.